Postgraduate Medicine

Volume 19 · Number 1

JANUARY · 1956

OFFICIAL JOURNAL OF THE INTERSTATE POSTGRADUATE MEDICAL ASSOCIATION

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The Johns Hopkins University School of Medicine and Hospital

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Postgraduate
Medicine

SPECIAL ISSUE

The Johns Hopkins University School of Medicine and Hospital

Foreword

THE Johns Hopkins Hospital is pleased and honored to be recognized, through the papers of its medical staff, in this special issue of POSTGRADUATE MEDICINE. The Johns Hopkins Hospital is proud of the scientific contributions of the members of its medical staff and recognizes that these contributions are the result of the intimate relationship the Hospital has with The Johns Hopkins University School of Medicine. This relationship and the medical investigation which it has produced lay the foundations for the distinguished work that has been done by Johns Hopkins in medical education, including the postgraduate education of physicians.

The papers presented in this issue cover a wide range of medical interests, problems and disciplines. It is noteworthy that the presentations bear closely on the day-to-day activities of medical and surgical practice, showing the closeness of our educational and research activities with the treatment of the patient.

RUSSELL A. NELSON, M.D.
Director, The Johns Hopkins Hospital

Management of Acute Streptococcal Infection in Relation to Rheumatic Fever and Glomerulonephritis

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LEIGHTON E. CLUFF

THE most serious consequences of group A streptococcus infection in man are acute rheumatic fever, chronic rheumatic heart disease and glomerulonephritis. Although suppurative complications are of immediate importance, they are as a whole more adequately and easily dealt with. As concerns the late nonsuppurative complications of streptococcal infection, i.e., rheumatic fever and glomerulonephritis, their pathogenesis is poorly understood and their treatment is therefore inadequate. Much has been written about the treatment of sequelae of acute streptococcal infection, but there is no unanimity concerning an effective therapeutic regimen. Attention will, therefore, be focused on the management of the acute infection because its treatment offers the only current hope of controlling rheumatic fever and glomerulonephritis. By preventing and perhaps by shortening or terminating the infection, it is often possible to allay the development of acute rheumatic fever and glomerulonephritis.

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Pharyngitis

Acute pharyngitis and tonsillitis are the streptococcal infections seen most often. The clinical differentiation of acute streptococcal infections and other infections of the throat is difficult. Criteria utilized are the presence of an exudate, fever, lymph node enlargement and leukocytosis. If all of these features are required for diagnosis of acute streptococcal sore throat, an erroneous diagnosis will infrequently be made. However, of greater importance, a large number of streptococcal infections will remain undiagnosed and possibly untreated. Because of the importance of treating streptococcal infections, it is necessary to suspect any acute pharyngitis as possibly

being due to group A streptococcus. If acute pharyngitis always is treated as though it were streptococcal in origin, consideration must be given to the hazard involved in treating a number of patients unnecessarily.

The incidence of acute rheumatic fever following proved streptococcal infection is estimated to be 3 per cent.[1] A history of pharyngitis or other infection frequently cannot be obtained in cases of acute rheumatic fever or glomerulonephritis. This must mean that a number of minor infections of the upper part of the respiratory tract go unattended and untreated. With this group, the physician has no opportunity to deal effectively except in epidemic or special circumstances. However, many patients with symptoms and signs of pharyngitis may not be treated because of the seeming insignificance of the disease. Undoubtedly, many of these mild infections are streptococcal in origin and can result in rheumatic fever or glomerulonephritis.

In order to adopt a policy which will not allow indiscriminate antibiotic treatment and yet will effectively manage the majority of streptococcal infections, any patient who has a *febrile pharyngitis*, whether associated with leukocytosis, exudation or lymphadenopathy, should be treated as though he had a streptococcal infection. Undoubtedly, some patients without streptococcal infection will be treated. However, the hazards of such a therapeutic program are not great. The incidence of sensitivity reactions to penicillin given for a short period of time is about 0.5 per cent.[2] A penicillin reaction may be caused unnecessarily; however, this is of less consequence than failure to treat a streptococcal infection which may lead to serious cardiac or renal disease.

By selecting patients with febrile pharyngitis, most patients with common cold and other respiratory diseases of viral origin will be excluded from therapy. Viral infections of the respiratory tract are characterized most often by coryza, sneezing, cough and laryngitis. Pharyngitis may be present in cases of viral infection, but usually not as a primary manifestation. If facilities are available, a throat culture should be obtained. Treatment begun after the culture is taken can be discontinued if the culture is negative for hemolytic streptococci after incubation for 24 hours.

When group A streptococcus pharyngitis develops in a member of a group, in a family in particular, it is likely that other members are harboring the same organism. Although it might seem superfluous to treat these carriers, such a procedure will prevent the development of streptococcal infection in other members of the group. This program of epidemiologic control is of greatest importance in a family in which rheumatic fever is known to exist. In other circumstances, treatment of families is not necessarily indicated, as long as symptomatic infections are adequately cared for.

The response of a patient with streptococcal pharyngitis to treatment with penicillin is not always dramatic. Fever may subside gradually over a three to five day period, and clearing of pharyngeal exudate may be delayed. This does not indicate that therapy is ineffective; repeated cultures of the throat will show prompt disappearance of streptococci, and there is little doubt that specific antibiotic treatment gives maximal protection against the development of late complications.

Other Streptococcal Infections

Scarlet fever and erysipelas are known to be due to group A streptococci. The diagnosis of these infections is seldom difficult, and treatment can be readily instituted. Skin infections characterized by cellulitis and abscess formation are often caused by hemolytic streptococci. Impetigo contagiosa, wound and burn infections, paronychia, intertrigo, acute otitis media and sinusitis are other infections often due to group A streptococci. It is important to treat these infections energetically because they too can be followed by glomerulonephritis or rheumatic fever.

Late Complications of Streptococcal Infections

Rheumatic fever—The relationship of rheumatic fever to group A streptococcus infection is well established. No particular type of group A streptococcus has been found responsible. In fact, clinical experience indicates that in-

fection with any of the 40 or more types is capable of leading to the development of rheumatic fever. The patient who has had rheumatic fever is peculiarly susceptible to recurrence of the disease on subsequent exposure to streptococci, and it is of greatest importance to prevent the development of these infections in rheumatic patients. The most effective agent for this purpose is penicillin. Prophylactic therapy should be given over a very long period of time, perhaps throughout life. Although recurrence of rheumatic fever is not common in older age groups, it does occur. There is every reason to believe that streptococcal infection in adults, although not productive of recognizable rheumatic fever, can cause progression of rheumatic heart disease. When streptococcal infections occur in patients with rheumatic fever, they should be treated promptly and effectively.

As mentioned before, many patients with rheumatic fever and rheumatic heart disease will not have a past history of respiratory infection or a history of previous rheumatism. Such patients, at present, pose one of the most difficult problems in prevention of the disease. No effective means is available for detecting or treating them prior to the onset of serious illness. However, if the physician understands the seriousness of the problem, deals effectively with acute pharyngitis when it occurs, and adheres to a program of prophylaxis for rheumatic patients, serious heart disease can probably be prevented in many patients.

Recent studies[3] have indicated that the institution of penicillin treatment of acute streptococcal pharyngitis nine days after the onset of the infection can significantly reduce the subsequent development of rheumatic fever. Therefore, treatment of patients with acute pharyngitis should be instituted even though several days may have elapsed since onset of symptoms.

A patient with acute rheumatic fever should probably be treated with penicillin initially, even though there is no evidence of streptococcal infection. There is no controlled study which will validate this suggestion, but such a program seems worthwhile, particularly if the patient has not been receiving penicillin as a prophylactic and has not had recent therapy for a streptococcal infection. When the patient with acute rheumatic fever is hospitalized he is likely to be exposed to many persons who are streptococcus carriers, and penicillin prophylaxis should be initiated promptly and should be continued.

Acute hemorrhagic glomerulonephritis—In 1935 Longcope, Bordley and Lukens[4] wrote. ". . . . experiences suggest that the patient who has once recovered from an attack of acute hemorrhagic nephritis is no longer susceptible to a recurrence of the disease when he contracts an infection due to hemolytic streptococci." The situation is different with rheumatic fever, as stated previously, in that the rheumatic patient is peculiarly susceptible to recurrence of rheumatic fever upon exposure to infection by hemolytic streptococci.

Type 12 and type 4 group A streptococci are responsible for most if not all instances of a common type of acute glomerulonephritis.[5] The insusceptibility to recurrence of nephritis with subsequent streptococcal infection is probably due to the development of type-specific immunity to these nephrogenic streptococci. For this reason, prophylaxis against streptococcal infection can contribute little to the management of the patient who has once had acute hemorrhagic nephritis. The only way in which acute glomerulonephritis can be prevented is by prompt and adequate treatment of streptococcal infection when it develops and by the treatment of carriers of type 12 and type 4 streptococci.

When acute glomerulonephritis develops in a member of a group or family, it is important to treat the other members who are demonstrated by culture to be harboring hemolytic streptococci. Incidence of glomerulonephritis after infection with the type 12 streptococci is very high, and every effort should be made to prevent its occurrence by adequate therapy with penicillin. If facilities for culture are not available, it is wisest to treat the entire group as though all were infected.

Tonsillectomy

The concept of tonsillectomy for patients who have had acute rheumatic fever has gained

wide acceptance. The value of this procedure in protecting the person from subsequent streptococcal infection is open to serious doubt. It is a common clinical experience to find that attacks of streptococcal pharyngitis are as frequent following tonsillectomy as before, even though exudation in the pharynx may not appear. Therefore, the indications for tonsillectomy in patients with rheumatic fever are no different from those in others, and this procedure cannot be relied on as a prophylactic measure against streptococcal sore throat.

Bacterial Resistance

Of current concern is the problem of the development of resistant bacterial populations because of widespread penicillin prophylaxis. After following a number of patients on penicillin prophylaxis for several years, it has become evident that there has been no alteration in throat flora, as a rule, other than the elimination of hemolytic streptococci. Patients have not had difficulty with resistant organisms after having received prophylactic treatment for long periods of time.

Therapy and Prophylaxis

Sulfonamides are known to be effective as prophylactic agents against rheumatic fever. However, they have serious drawbacks for widespread use in comparison with penicillin: (1) Group A streptococci have become resistant to sulfonamides used widely in Naval recruits; (2) sulfonamides are bacteriostatic for hemolytic streptococci and therefore are incapable of eliminating the carrier state; (3) they are not suitable for therapy of streptococcal infection because of their inability to completely eradicate the organism, and (4) serious disease which is due to hypersensitivity has occurred in cases in which sulfonamides were being used.

Not enough experience is available to evaluate fully the "broad-spectrum" antibiotics for prophylactic purposes. However, they have essentially the same drawbacks as sulfonamides, and the expense is usually prohibitive.

Penicillin is by far the most effective prophylactic agent available against streptococcal infection. Group A streptococci rarely if ever become resistant to penicillin. The hemolytic streptococci are very sensitive to even small doses of penicillin, which is bacteriolytic. Hypersensitivity reactions to penicillin do occur, but they seldom are serious.

The recommendations of the American Heart Association for the management of streptococcal pharyngitis are most acceptable. In the treatment of these infections, one of the following schedules is used.

Schedule 1—One intramuscular injection of 600,000 units of benzathine penicillin G (BICILLIN®) is used for children, and a similar injection of 600,000 to 900,000 units is used for adults.

Schedule 2—Procaine penicillin is administered intramuscularly every third day until three doses have been given. The individual dose is 300,000 units for children and 600,000 units for adults.

Schedule 3—A dose of 250,000 units of penicillin is administered orally, three times a day for 10 days, to children and adults.

One of the following schedules is used in the prophylaxis against streptococcal infection in cases of rheumatic heart disease or active or inactive rheumatic fever.

Schedule 1—A dose of 200,000 to 250,000 units of penicillin is administered orally once a day, either before breakfast or on an empty stomach.

Schedule 2—Benzathine penicillin G is administered intramuscularly, once a month, in doses of 1,200,000 units.

Schedule 3—An oral dose of 0.5 to 1.0 gm. of sulfadiazine is administered every morning or once a day.

Sensitivity reactions, characterized by fever or rash, may develop while a patient is receiving penicillin or a sulfonamide. If this occurs, it is best to discontinue the responsible agent and substitute another. However, it is not unusual for the sensitivity reaction to subside spontaneously even though administration of the original drug is continued. If sensitivity reactions to penicillin and sulfonamide develop, a broad-spectrum antibiotic such as AUREOMYCIN® or TERRAMYCIN® may be used. Prophylaxis with the latter agents can be accomplished with 0.5 gm. given orally each day.

Summary

The prevention of rheumatic fever and glomerulonephritis is dependent on the prompt and effective treatment of acute streptococcal infection. The diagnosis and treatment of the classic septic sore throat due to group A streptococcus is not difficult. The development of late nonsuppurative complications of streptococcal infection after mild febrile pharyngitis indicates the need for treating all such infections as though they were due to streptococci. Only in this way will it be possible to reduce further the incidence of rheumatic heart disease. Those instances of rheumatic disease and hemorrhagic nephritis which develop in patients without a history of preceding infection are still beyond the control of the physician.

Continuous prophylactic antibiotic treatment should be given to every patient with active or inactive rheumatic fever, including chorea, and to every patient with rheumatic heart disease.

For reasons discussed, prophylactic antibiotic treatment is unnecessary in the management of the patient who has recovered from acute hemorrhagic nephritis.

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Postgraduate Clinical NOTES

42. TREATMENT OF PARKINSONISM

There is no specific treatment for parkinsonism. All effort is directed to the alleviation of signs and symptoms, particularly of the tremor and the muscular rigidity. Little can be done for the syndrome occurring in cerebral arteriosclerosis, although there may be some spontaneous if temporary recovery of arteriosclerotic signs on partial or complete reestablishment of circulation in the brain. The treatment, then, is directed mainly to the progressive syndrome. The two groups of drugs now generally used are the atropin-belladonna preparations, which mainly affect the tremor, and the antihistamine preparations which mainly influence the muscular rigidity. Of the former hyoscin or scopolamin seem the most effective. The Bulgarian root extract or the synthetic preparations containing its ingredients are sometimes more effective in chronic encephalitic parkinsonism. These drugs may also help to stem the distressing salivation. A patient occasionally does not tolerate one or another preparation and one may have to try various substitutes. Numerous antihistaminic preparations are available and each has its adherents. Artane, an American preparation, and parpanit, a French one, seem to be most effective, but there may be others which are equally good. Ordinarily the medication can be continued with impunity practically indefinitely, unless one shows special intolerance of the drugs. Several attempts have been made to make short cuts, as it were, to "cure" parkinsonism by means of brain surgery. The results, at first enthusiastically proclaimed, have not justified the hopes they inspired.

Israel S. Wechsler, *Harofé Haivri*, Volume 2, 1954, p. 204

Surgical Treatment of Aortic Aneurysm and Aortic Thrombosis

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THE contributions to surgery of the great vessels by Gross, Crafoord, Blalock and others have been responsible for instruments, technics and surgical philosophy which make possible a direct attack on diseases of the aorta. Excision of aortic aneurysm and thrombosis is now the method of choice, whereas it formerly was thought to be associated with such risk as hardly to be considered. Development of satisfactory means of obtaining and preserving aortic homografts facilitated the use of such grafts when necessary for reconstruction of aortic continuity. Direct attack on these lesions has produced early results which promise much greater benefit to the patient than previous, less definitive methods.

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Aortic Aneurysm

Aortic aneurysms are the result principally of two diseases, arteriosclerosis and syphilis. Occasional ones are congenital in origin or are caused by trauma or bacterial infection, but in most clinical respects these resemble aneurysms due to syphilis. The clinical differences between syphilitic and arteriosclerotic aneurysms are striking (figure 1). Those due to syphilis usually occur in the thoracic aorta and almost always are above the origin of the renal arteries. They often are associated with pain from pressure on the spinal nerves or obstruction to the esophagus or tracheobronchial tree. They occur in middle-aged persons, and have a notoriously poor prognosis. In a review of 633 cases of aneurysm, Kampmaier[1] found that only 18 of the patients lived for two years after the onset of symptoms. The average duration of life from the onset of symptoms to death was between six and nine months, depending on the site of the aneurysm. Aneurysms due to arteriosclerosis occur in older persons, almost always below the renal arteries, are associated with fewer symptoms,

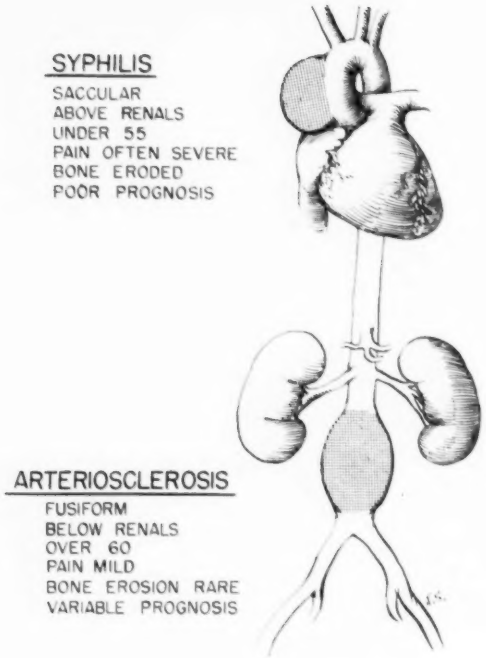


FIGURE 1. Sites and clinical characteristics of the two principal types of aortic aneurysm. Occasional aneurysms due to trauma or bacterial infection resemble those due to syphilis in many respects.

(Figures 1, 3 and 11 from Bahnson, H. T.: Considerations in excision of aortic aneurysms. Ann. Surg. 138:377, 1953.)

are almost always fusiform in nature, and have a variable but better prognosis.

Estes[2] made a follow-up study of 102 patients with abdominal aneurysm who were seen at the Mayo Clinic, and he found that 50 per cent died within one year and 90 per cent within eight years. Of 49 patients in whom the cause of death could be determined by autopsy, 63.3 per cent died of rupture of the aneurysm. One can estimate from these data that one of five patients with an abdominal aortic aneurysm will die of rupture of the aneurysm within one year, and that half will die of rupture within five years (figure 2). The lower line in figure 2 represents the life expectancy of a normal population aged 65 years, which was the average age of patients with aneurysms reported by Estes.

The incidence of the two types of aneurysms is changing. Syphilitic aneurysms are becoming uncommon as a result of better diagnosis and treatment of syphilis, whereas arteriosclerotic aneurysms are more frequent by virtue of the increase in the life span of the human being. Maniglia and Gregory[3] reviewed the autopsies performed at the Hahnemann Hospital during the period from 1906 to 1951. The actual number of aneurysms per 1000 autopsies did not change significantly, but the relative incidence changed from 3

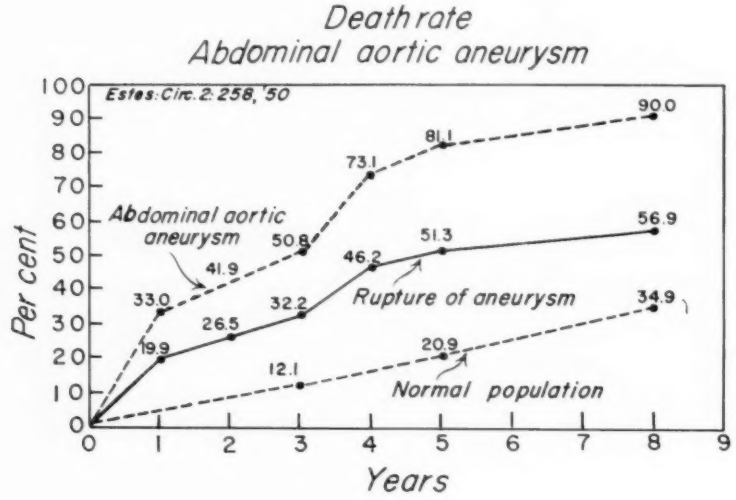


FIGURE 2. Upper curve and figures are based on a follow-up study of 102 patients with abdominal aneurysm by Estes.[2] Lower curve is estimated from life insurance data. Middle curve is computed from follow-up data and from Estes' observation that death was due to rupture of the aneurysm in 63.3 per cent of 49 cases of aneurysm in which the cause of death was known. The middle curve is the important one for estimation of the prognosis.

syphilitic to 1 arteriosclerotic aneurysm between 1906 and 1931, to 2.5 arteriosclerotic to 1 syphilitic aneurysm between 1949 and 1951.

Both types of aneurysms are amenable to excision.[4-7] Syphilitic aneurysms, although part of a generalized disease, usually represent localized blowouts. If the localized blowout can be excised or patched, the remaining cardiovascular system may be adequate for many years of function. On the other hand, arteriosclerotic aneurysms, by virtue of their almost invariable site in the terminal portion of the abdominal aorta, can be excised during occlusion of the aorta just below the renal arteries, and a graft may be inserted.

Three principles underlie the treatment of aortic aneurysms: (1) The tendency for a hollow viscus to rupture or the strain upon its wall is directly related to its diameter. Hence the first principle is to reduce the diameter of the vessel and the tension on its walls. (2) The aneurysm can be no stronger than its weakest area; hence, any thin, unstable and weak portion should be removed or adequately reinforced. (3) Finally, whenever possible, the tumor should be removed, particularly when it is in the thorax and is causing respiratory or esophageal obstruction. The means of carrying out these principles differs in various parts of the aorta, and can best be illustrated by a brief description of the operative procedures which have been used at The Johns Hopkins Hospital.

Aneurysms situated in the ascending arch of the aorta must have a narrow mouth which can be isolated and occluded, since this portion of the aorta can be occluded only for a brief instant. Whenever possible, dissection is begun over the less involved portion of the aorta and then carried to the neck of the aneurysm. The peripheral portion of the aneurysm is not dissected from the lung and adjacent tissues until its mouth is occluded. Figure 3 shows a syphilitic aneurysm of the ascending aorta which caused respiratory and esophageal obstruction in a 54 year old Negro man. The aortogram was made by inserting a small polyethylene catheter through the femoral artery and advancing it into the aneurysm. After

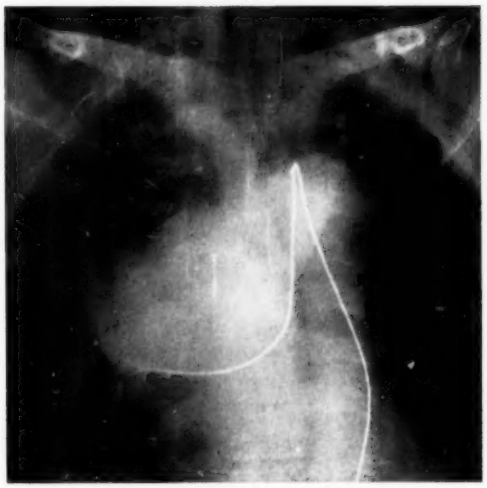


FIGURE 3. Aortogram showing opacification of aneurysm by contrast medium injected through a catheter inserted percutaneously into a femoral artery.

mobilization of the mouth of the aneurysm and the adjacent aorta, a clamp was placed on this region, the mouth was incised, and the aorta was sutured with multiple sutures of fine silk (figure 4). The patient made an uneventful recovery.

In the more distal portion of the aorta, the vessel may be occluded for increasingly longer periods. The aneurysm shown in figure 5 appeared following an automobile accident. The usual site for an aneurysm due to such trauma is at the distal end of the aortic arch near the mouth of the left subclavian artery. The sudden stop of the body with briefly continued motion of the heart causes a tear which is usually fatal, but in some instances is small enough to be contained by adjacent adventitia and is initially sealed by a clot. In this patient there was no evidence of syphilis or any cause other than the trauma. She had been treated previously by cellophane wrapping but continued to have pain in the region and hoarseness, and angiocardiography suggested that the aneurysm had enlarged.

The aorta was occluded just proximal to the left common carotid artery and distal to the aneurysm for seven minutes while the aneu-

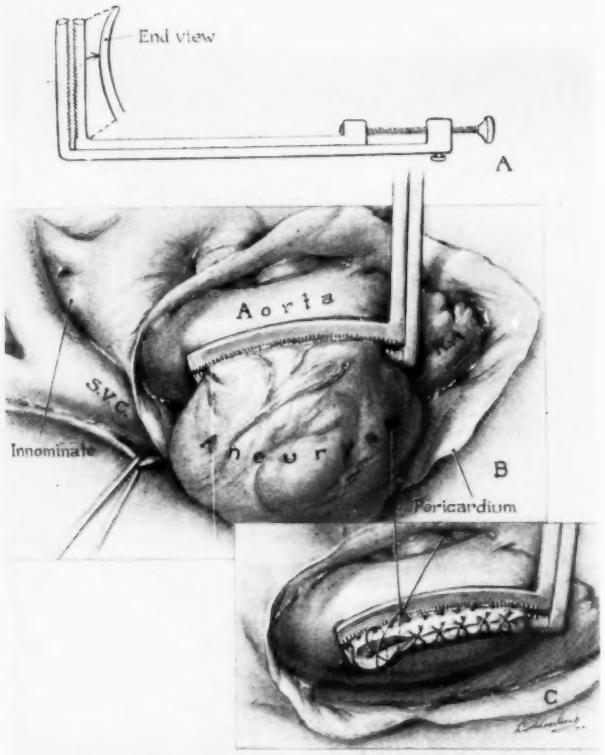


FIGURE 4. Operative exposure of aneurysm of the ascending aorta through the third right interspace and a vertically split sternum. The mouth of the aneurysm has been dissected free and a specially constructed clamp has been applied. After excision, the aneurysm mouth was closed with multiple interrupted sutures of 0000 silk.

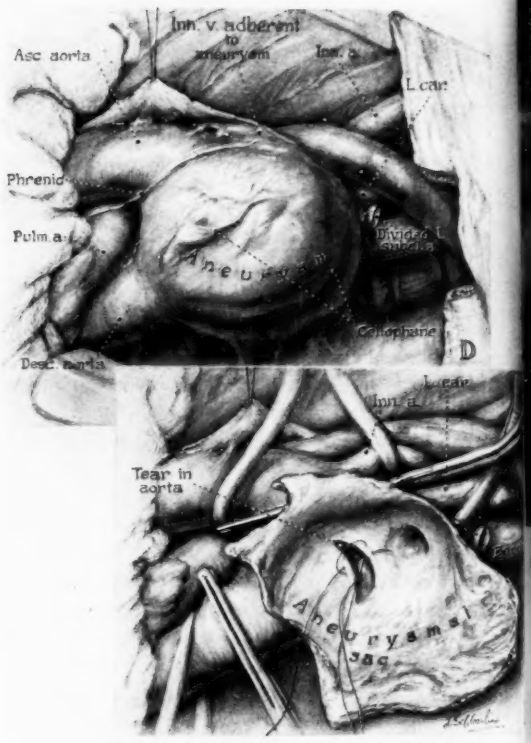


FIGURE 5. Posterolateral exposure of aortic arch and mediastinum. The aneurysm arose from the distal portion of the aortic arch. It was opened and excised after the aorta was clamped proximally and distally. The circumferential tear in the aorta was sutured, and the adjacent aneurysmal sac was sutured over the defect.

(Figures 5, 6, 7, 9 and 10 from Bahnson, H. T.: Definitive treatment of saccular aneurysms of aorta with excision of sac and aortic suture. Surg., Gynec. & Obst. 96:383, 1953.)

rysm was opened and suture of the mouth was begun. This period probably approaches the upper limit of occlusion in this region, for at the end of seven minutes the patient had frequent extrasystoles, and the blood pressure began to fall. The mouth of the aneurysm was held shut manually, the clamps were removed, and suture was completed by sewing down a small flap of the aneurysm over the remaining orifice. The patient has been well and essentially asymptomatic in the two and a half years since the operation.

Aneurysms in the thoracic aorta may be handled in one of two ways. Some are distinctly saccular and can be treated by occlusion of the aorta above and below, excision of the aneurysm, and suture of the mouth of the aneurysm. Some are more fusiform in nature and require the insertion of a graft. The roentgenogram in figure 6 shows an aneurysm of the upper part of the thoracic aorta which caused intractable pain from pressure on the spinal nerves in a 41 year old man. He had been temporarily relieved by electrothermic coagulation of the aneurysm by the method of Blakemore and King[8] with fine wire which was heated inside the aneurysm.

The aneurysm enlarged, and excision was thought indicated. At operation, the aorta was occluded above and below the aneurysm for

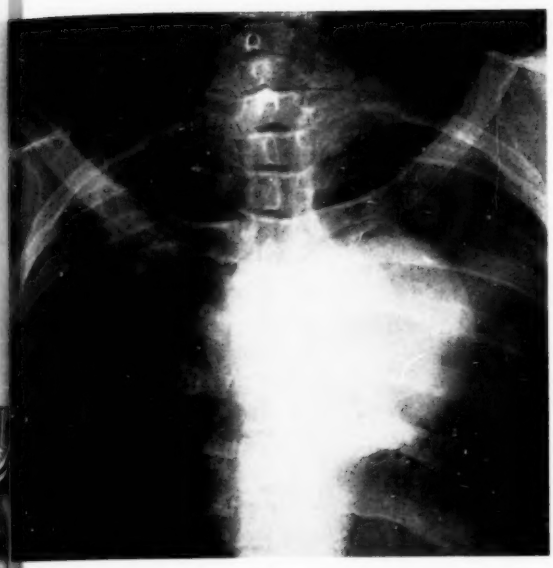


FIGURE 6. Roentgenogram of thorax of a 41 year old man with intractable pain which had been temporarily relieved by electrothermic coagulation one year previously. A tuberculous cavity was present in the apex of the right lung.

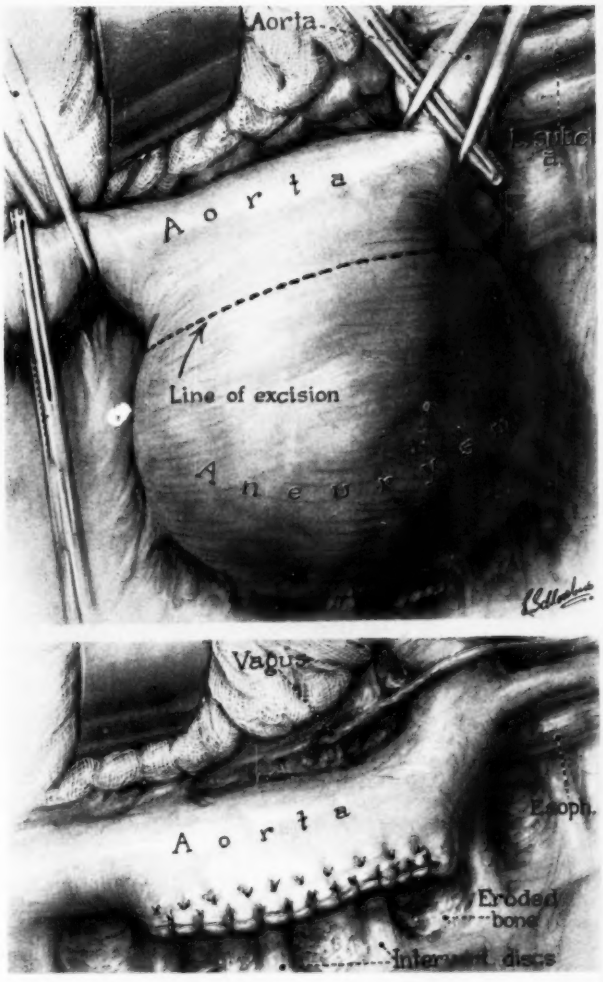


FIGURE 7 *(right)*. Aneurysm of upper part of thoracic aorta and reconstruction after excision. Eroded vertebral bodies can be seen.

20 minutes while an incision was made in the sac and the aortic opening closed (figure 7). A discrete line of demarcation could be seen between the mouth of the aneurysm and the diseased but functionally adequate adjacent aorta. At the time of this operation, the patient had a tuberculous cavity in the apex of the right lung, but it was felt that, with modern antibiotic treatment of the tuberculosis, the cavitary disease was of secondary importance. Antibiotics were administered for a long time after the operation for the aneurysm, and the upper lobe of the right lung, which was the site of the tuberculous cavity, was removed later. At present, the patient is doing well.

We had hoped to treat the aneurysm shown in figure 8 in a similar manner but found the entire aorta diseased and could discern no

FIGURE 8 *(right)*. Roentgenogram of excised specimen and nylon graft in case of aneurysm of the midthoracic portion of the aorta.

line of demarcation between the aneurysm and the aorta. As a homograft was not prepared, we sutured in a tube of nylon, as shown on the side of the photograph, and the result was completely satisfactory. In this case, the aorta was occluded for 24 minutes without evidence of later embarrassment to the lower portion of the body.

Some of the aneurysms have been quite large. Figure 9 shows a 45 year old man with an aneurysm of the upper part of the abdominal aorta. In spite of two apparently satisfactory wiring procedures over an eight month interval, the aneurysm continued to enlarge. The aorta and its abdominal branches were occluded for 37 minutes while the sac was incised and the mouth sutured (figure 10). The patient had an eventful and prolonged convalescence, but is now well three years later.

With rare exceptions, arteriosclerotic aneurysms have been localized to the aorta below the renal arteries, and there has been a sufficient length of aorta between the renal arteries and the aneurysm to allow occlusion. It is not generally appreciated that the bifurcation of the aorta is approximately at the level of the umbilicus, so that when an aneurysm is felt in the upper part of the abdomen there is no reason to believe that it extends above the renal arteries.

At operation, the aorta above the aneurysm and the iliac vessels distally are usually easily mobilized. The aneurysm itself is not extensively mobilized prior to actual excision because of some danger of rupture but chiefly because of the possibility of dislodging a thrombus into the arteries of the lower extremities. Once the aorta is occluded proximally and the iliac arteries distally, the aorta may be divided and the aneurysm readily dissected out of its bed (figure 11). Reconstruction is by means of a graft between the aorta proximally and the iliac arteries distally (figure 12b). In some instances, a straight segment may be used between the ends of the aorta proximal to the bifurcation.

We have operated on 26 patients in whom a saccular aneurysm was present in the chest or upper part of the abdomen. In 24 of the 26 cases, the aneurysm was due to syphilis. In one of the two remaining cases, it resulted from an automobile accident, and in the remaining case it was due to arteriosclerosis. Eight of the 26 patients have died, and the remaining 18 are well.

We also have operated on 34 patients with arteriosclerotic aneurysms. The ages of these patients ranged up to 76 years. Four of the patients died as a result of an elective operation, two died after an emergency operation for severe shock due to rupture of the aneurysm, and two died late in life of coronary artery disease. Another patient lost a leg because of a dislodged clot. This patient and the 25 others are now well.

Aortic Thrombosis

Thrombosis of the aorta is usually the result of arteriosclerosis, and as such is found with increasing frequency in older persons. In young men, however, it produces a distinct clinical picture commonly called the Leriche syndrome. The disease probably begins in the common iliac arteries where arteriosclerosis usually first becomes apparent. The initial lesion is probably an arteriosclerotic narrowing on which thrombosis becomes superimposed. The occlusion may be limited to one or both iliac arteries, but frequently progresses to involve both of these arteries and the terminal aorta.

Symptoms are due to ischemia of the legs which produces intermittent claudication and pain in the low back or abdomen. Many patients with aortic thrombosis have been seen initially by orthopedists or neurosurgeons because of the low back pain. Several features distinguish this pain clinically from that caused by neuromuscular conditions. When the stenosis is localized to the common iliac artery, the almost invariable picture is that of pain in the buttocks on walking. When the entire aorta is obstructed, the pain is more diffuse in nature and occurs in the thighs and calves, although even then it may first appear in the buttocks. The important feature about pain in this condition is that it is caused by exercise and quickly relieved by rest. Bending, coughing and sneezing do not accentuate the pain, which might be called angina of the buttocks.

FIGURE 9. Photograph of patient with aneurysm in upper part of abdominal aorta with pulsating mass in the left flank which encroached on the costal margin above and on the iliac crest below.

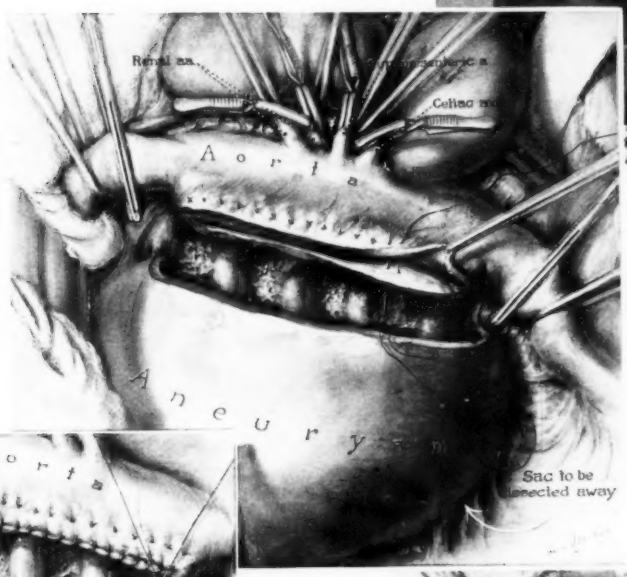
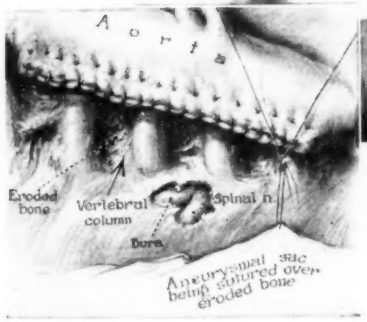


FIGURE 10. Exposure of abdominal aneurysm through the bed of the tenth rib and upper abdominal incision. The aorta and its branches were occluded, the mouth of the aneurysm was incised and the opening was closed with multiple sutures of fine silk. The vertebral bodies, spinal nerves and dura were exposed to blood.



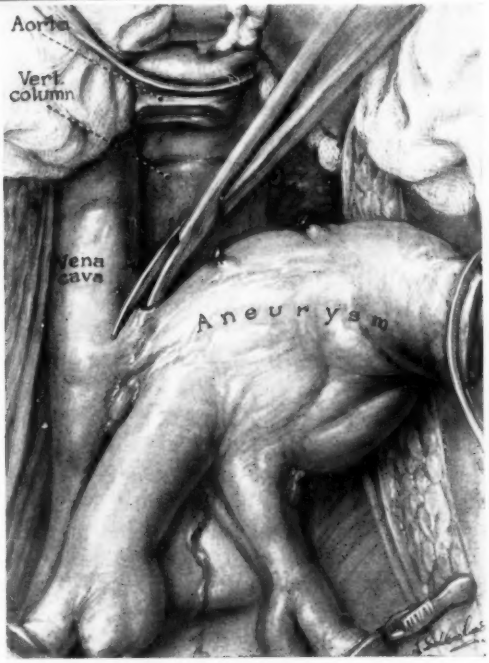


FIGURE 11. The aorta and the external iliac arteries have been occluded and the aneurysm is being removed. Adherence to the vena cava has been prominent in all cases of this type of aneurysm.

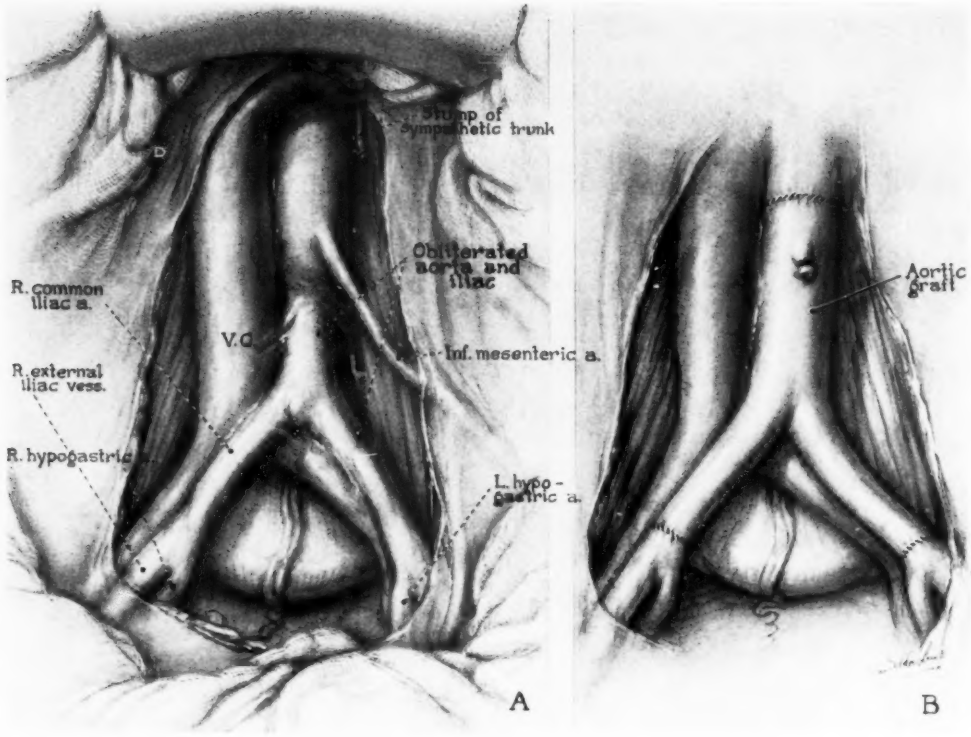


FIGURE 12. Thrombosis of left and marked narrowing of right common iliac artery. During manipulation, complete thrombosis occurred on the right side. Operation included excision of the terminal aorta and common iliac arteries, and replacement with a homograft.

The diagnosis is confirmed by absent or weak femoral pulses. Sometimes a murmur can be heard over the groin when stenosis is present or when the collateral channels are enlarged. An additional symptom is impotentia erigendi, or the inability to obtain or maintain an erection. This is not invariably present, however, for one of our patients became the father of a child after thrombosis of the aorta appeared. Since the impotentia appears at an age when men are becoming impotent for other reasons, the impotentia itself is of little diagnostic aid.

In all of our cases of aortic thrombosis, we have obtained aortograms in order to localize the site of obstruction. This readily demonstrates the height to which the thrombosis extends. To demonstrate the distal end is more difficult. If the film is exposed after several seconds delay, the distal segment often may be seen filled through collateral vessels.

Some of the patients have been treated by sympathectomy with generally unsatisfactory results. Much better treatment is excision of the involved area and grafting. This is a relatively simple procedure, and a good result can be expected if one can obtain a satisfactory vessel distally. It is surprising how frequently the thrombosis stops in the common iliac artery, and the hypogastric and external iliac arteries are nicely patent. In some cases, however, one must supplant the entire aorta and iliac arteries as far as the femoral arteries. If a good vessel is not present distally, the chances of getting into difficulty with circulation to the leg after operation are consider-

able. When we are unable to see the distal vessel on an aortogram, our policy is to make an incision in the groin and determine whether or not a satisfactory patent femoral artery is present. If it is, a good result can be expected after excision and grafting, and we proceed to do this. We have not yet encountered difficulty in obtaining a satisfactory vessel proximal to the obstruction.

Figure 12 illustrates a case of a 47 year old man who first noted significant difficulty when he was unable to climb hills while deer hunting. The left common iliac artery was occluded. The right iliac artery was patent at the time the arteriogram was made, and when the region was explored a thrill was palpable over the distal portion of the artery. During isolation of the vessels, the thrill disappeared, and examination of the specimen showed a fresh thrombus occluding the right common iliac artery proximal to an area of extreme arteriosclerotic narrowing. The operative manipulation simply hastened the process which would have occurred spontaneously. The terminal aorta from just above the inferior mesenteric artery, through the bifurcation and out to both common iliac arteries, was excised and replaced with a homograft. The patient has obtained a good result and has resumed deer hunting.

Thrombosis of the iliac arteries with or without terminal aortic thrombosis has been excised and the aorta reconstructed with a homograft in 17 patients. In one patient, for unexplained reasons, late thrombosis occurred in one limb of the bifurcation graft. In two others, satisfactory anastomosis could not be obtained to one limb of the graft and thrombosis occurred in the early postoperative period. In all three of these patients the contralateral limb has been improved and neither extremity has been made worse. In all the other patients the distal pulses have been restored and improvement has occurred in use of the legs.

Grafts

Three types of grafts have been employed in this group of patients with aneurysms or aortic thrombosis. In the first patient treated, a graft was used which had been preserved in tissue culture medium as originally described by Gross, Bill and Peirce.[9] All subsequent homografts have been frozen and dried.[10] The initial ones were obtained aseptically, but more recently ethylene oxide has been used to sterilize grafts taken without sterile precautions at autopsy. After quick freezing, the grafts are stored in a carbon dioxide icebox until they are later dried under low vacuum from the frozen condition and stored in the dry state.

Both types of homografts have been completely satisfactory. The frozen dried grafts have a distinct advantage in that they can be easily transported and kept almost indefinitely. In 10 patients with aneurysms for whom we did not have homografts, tubes made from nylon fabric have been inserted. In one of these patients, the aneurysm was in the thoracic aorta. Use of such material is based on work done by Blakemore and Voorhees with VINYON-N®. The synthetic fabric has several advantages, the principal ones being the absolute sterility and ease of procurement. Such materials are under active investigation by several workers at the present time and hold considerable promise for future vascular replacement.[11]

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Proteolytic Enzymes in Inflammation: Rationale for Use

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THE mechanics of inflammation are still poorly understood, although it is one of the most common conditions seen by the surgeon. This dynamic process never reaches equilibrium, since inflammation either spreads or recedes, depending on local interplay of cells and chemical compounds. The cellulitis seen initially may be resolved by the action of the humoral forces of the body. Partial inhibition of the operation of these substances results in progression of cellulitis to abscess. Complete failure of action ends in invasive spread of the bacteria.

The antibacterial drugs, a powerful aid to the action of the humoral forces, have permitted singular advances in the treatment of inflammation, particularly cellulitis, since their introduction into use. The results in the treatment of abscess have not been as brilliant. The action of many of the antibacterial drugs on selected bacteria is greater in vitro than in vivo. One may conclude, therefore, that certain factors limiting the action of these agents exist at the site of inflammation. Application of the knowledge of bacterial metabolism and physiology in clinical problems indicates that relationships favorable to the bacteria present may be modified or removed. Selected proteolytic enzymes may offer physical and chemical changes in the inflammatory curtain and permit a more complete realization of the therapeutic potential of the humoral forces and the antibacterial agents.

The therapeutic effect of an antibacterial drug in inflammation depends on (1) the type and number of bacteria present, (2) the susceptibility of the microorganisms, (3) the concentration at the affected site, (4) the chemical environment at the involved area, and (5) the degree of immunity of the host. The concentration of the drug at the affected site and the chemical environment in which it acts may be changed by the proteolytic en-

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zymes. To understand how these factors can be influenced necessitates a review of the present knowledge of inflammation.

The acute inflammatory reaction is characterized by excessive local dilatation of the capillaries due to a chemical compound the nature of which is not definitely known. This substance may be an H substance similar to histamine,[1-3] a less diffusible H colloid,[3] histamine,[4-6] or a slow-reacting substance.[6] Certain changes in the capillaries also can be produced by the administration of polypeptides extracted from tissues or the inflammatory exudates.[7-10]

The capillary endothelium is injured by one or more of these chemical compounds. Permeability is thereby increased, allowing fluid to pass more freely into the tissues. Polymorphonuclear neutrophilic leukocytes and later mononuclear cells enter the inflammation area.

Fibrin is formed in the fluid from fibrinogen, diffusing from the blood stream through the action of thrombin liberated from disintegrated blood platelets. Hughes[11,12] has demonstrated that the wall of fibrin formed in and about the site of inflammation is remarkably selective in permeability. When filtered under pressure, albumin will pass through but globulin, containing antibodies, will not. Some bacterial toxins will diffuse slowly, although most products of such origin will not. Bacteria are restrained but polymorphonuclear neutrophilic leukocytes pass readily. Fibrin, apparently, usually prevents the spread of bacteria, but protects the bacteria from immune bodies in the globulin fraction of the blood serum.

Most bacteria are ingested by phagocytic cells as soon as the microorganisms enter the body.[13] Local resting-wandering cells are an important part of the reaction of the body in inflammation. Tompkins[14] and Tompkins and Grillo,[15] in studying the relationship of the chemical environment to these cells, reported that it seems probable that the conversion of local resting-wandering cells into macrophages in injured areas is influenced by potassium liberated in the area.

Phagocytosis is best effected on a surface when leukocytes can trap bacteria against an opposing surface such as the wall of the tissue involved or other leukocytes.[16-18] Surface phagocytosis is relatively inefficient in open cavities such as those formed by peritoneum, pleura, pericardium and meninges.[18] The same condition prevails in the center of an established abscess.[18] Leukocytes are not good phagocytes in fluid.[18] Where an adequate supply of oxygen is lacking, the leukocytes become nonmotile and lose their power of phagocytosis.[19]

After the studies of Metschnikoff[20] were published, it was believed that phagocytosis was the most important part of the inflammatory reaction. The ingestion of bacteria by phagocytes, however, does not necessarily imply protection for the host. Conversely, Roux and Jones[21] demonstrated that living phagocytes were able to protect ingested bacteria from the action of destructive substances in the surrounding fluid and strong homologous antiserum. A number of investigators using different microorganisms have shown that intracellular bacteria are protected from antibacterial drugs. Magoffin and Spink[22] observed protection of intracellular *Brucella* from the rapid lethal action of streptomycin alone and in combination with other antibiotics. It was found by Suter[23] that the concentration of streptomycin required to inhibit the growth of tubercle bacilli in phagocytes was about 100 times greater than that required to suppress extracellular multiplication in TWEEN®-albumin medium. By contrast, this minimal inhibitory concentration of isonicotinic acid hydrazide was the same for extracellular growth in Tween-albumin medium and for intracellular growth in tissue culture. Results reported by Mackaness[24] who used streptomycin are similar in that 50 times the concentration of the drug required to inhibit the growth of tubercle bacilli in vitro did not kill these bacteria in macrophages in 10 days. Mackaness and Smith[25] pointed out that streptomycin penetrates cells only in limited fashion while isoniazid has the capacity to kill intracellular tubercle bacilli rapidly.

Leukocytes can produce large amounts of lactic acid and it is possible that the intracellular pH is lowered following phagocytosis.[13]

Death of the leukocytes releases bacteria and chemical compounds into the surrounding environment. The pH of some inflammatory exudates is decreased to 5.3 from lactic acid derived from inflammatory cells and fixed tissue cells. Dubos[26,27] demonstrated that lactic acid and some of the other short-chain aliphatic acids inhibited the multiplication of staphylococci and tubercle bacilli at acid reactions presumably prevailing in inflammatory areas while the ketone bodies stimulated growth. In addition, the ketone bodies afforded some protection against the inhibitory effect of lactic and acetic acids at acid reactions. Metabolic disturbances of the host producing a ketosis may depress the antimicrobial action of lactic acid and provide bacteria with factors to enhance their growth.

Dubos[28] reported that long-chain fatty acids exhibited both inhibitory and stimulatory effects on the growth of tubercle bacilli and of a certain unidentified *Micrococcus*. The toxicity of the fatty acids was much reduced by esterification or the addition of crystalline serum albumin.

Nieman[29] likewise pointed out that saturated and unsaturated fatty acids in low concentrations may inhibit or promote the growth of microorganisms. The effect observed depended on the concentration and nature of the fatty acid and the bacteria involved.

Cellulitis progresses to formation of an abscess with concomitant obstruction of the arterial circulation by thrombi of fibrin. A deficiency of oxygen is produced at the site of inflammation. Blockage of the venous circulation produces an increased concentration of carbon dioxide and edema. Obstruction of the lymphatic circulation causes edema. The net result is death of tissue and ground substance.

Hydrolysis of this necrotic material by enzymes derived from bacteria, leukocytes and blood produces a cavity of pus. By this time, a wall of fibroblasts has formed about the affected area.

Pus is a mixture of biochemicals derived from the bacteria and the tissues of the host. The components are many, but only some have been identified and the action of only a few determined.

1. Bacteria, products of bacteria, and products of death of bacteria—Bacteria attacks living cells of tissue and ground substance. The enzymes which the microorganisms elaborate digest the complex chemical compounds present into simpler structures, some of which are useful as anabolites and some of which cause more injury to the host. A further amount of macromolecular substances is thus produced to undergo breakdown. The course of inflammation is greatly affected by the extracellular products or enzymes produced by gram-positive bacteria. The hemolytic *Streptococcus* makes streptokinase,[30] streptodornase[31] (which is actually a group of depolymerases), ribonuclease,[32] proteinase,[33] hyaluronidase,[34,35] streptolysin O,[36] and streptolysin S.[36] Pathogenic strains of staphylococci produce coagulase, staphylokinase and hyaluronidase.[36] *Clostridium welchii* makes alpha toxin, or lecithinase, collagenase and hyaluronidase.[36] Streptokinase and staphylokinase, by causing fibrinolysis, may spread the infection. Coagulase clots blood plasma, and the fibrin deposited about the staphylococci may prevent phagocytosis.[37] The hydrolysis of hyaluronic acid by hyaluronidase will increase the permeability of connective tissue and may influence the dissemination of bacteria and their toxic products. The observations of Crowley,[38] however, do not suggest that the production of hyaluronidase by streptococci is related to their virulence in man.

Dubos[39] has noted that bacteria in an area of inflammation are subject to countless influences. These vary with the particular bacteria present, the physiologic state of the host and the anatomic location of the inflammation. Small differences in physiochemical values have quantitative and survival effects on bacteria and qualitative consequences on serologic specificities, enzymatic properties and resistance to drugs.

With the death of bacteria, ribonucleoprotein, ribonucleic acid, desoxyribonucleoprotein and desoxyribonucleic acid are released by enzymatic digestion. Hydrolysis of these substances may provide material for enhancement of the inflammation.

2. Fibrin—The part of fibrin in inflamma-

tion has been discussed. In addition, bacteria enmeshed in masses of fibrin are not easily reached by the humoral forces or the antibacterial drugs.

3. White blood cells, living and dead—Phagocytosis and production of lactic acid have been considered. The dead leukocytes are a source of desoxyribonucleoprotein, desoxyribonucleic acid, ribonucleoprotein and ribonucleic acid. Desoxyribonucleoprotein and desoxyribonucleic acid produce a highly viscous pus and clumping of polymorphonuclear neutrophilic leukocytes. As the power of cellular motility is lost, the ability for phagocytosis is decreased.[40]

4. Red blood cells—Erythrocytes are present in varied number depending on the bacteria involved. In anthrax, red blood cells are a prominent feature since actual destruction of the wall of the capillary occurs. Agglutination of the erythrocytes adds mass to the debris.

5. Dead tissue cells—These cells are a source of nucleoproteins. The depolymerization of nucleoproteins produces many derivatives whose function is being slowly understood. Adenosine triphosphate[41] and adenine nucleotide,[42] of which the active principle is adenosine triphosphate, are potent vasodilators. Paralleling the suggestion of Barnard,[43] it may well be that desoxyribonucleoprotein depolymerized to the nucleotide stage, where a reactive furanose group is present, may act as a hemagglutinin and an aggressin, with potentiation of many ill effects of inflammation.

6. Glycoproteins and hyaluronic acid derived from the ground substance—Barnard[43] has reported that partial depolymerization of the glycoproteins and hyaluronic acid in ground substance by glycolytic enzymes can serve as important sources of hemagglutinins and aggressins. A resonating furanose group was common to the compound causing both reactions. Hemagglutination produces thrombosis in the capillaries with consequent anoxia and cell death. Tissue cell death was also caused by direct aggressin attack.

The course of inflammation may be altered in the stage of cellulitis or abscess by the proteolytic enzymes. The stage and the substrates present determine the enzyme and method.

Fibrinolysis, indirectly effected by streptokinase, provides an avenue of attack on one of the components of the inflammatory barrier.[44] The underlying principles by which the administration of streptokinase intramuscularly in conjunction with the systemic use of the antibacterial drugs produces a reversal of the inflammatory reaction and edema are not known. Streptokinase, however, activates the plasminogen in the euglobulin fraction of the blood to plasmin. Plasmin causes lysis of fibrin. With this property in mind, patients with varied types of inflammation were treated by intramuscular injection of streptokinase.

VARIDASE®, which contains streptokinase and streptodornase, is used since streptokinase in pure preparation has not yet been made. The streptodornase can be disregarded for purposes of injection. Varidase is dissolved in physiologic saline so that the final concentration is 10,000 units of streptokinase per cubic centimeter. The solution must be freshly made daily and should be stored in a refrigerator when not being used.

Five thousand units of streptokinase in 0.5 cc. of physiologic saline is injected intramuscularly twice a day for a minimum of three days. An antibacterial drug must be given concurrently. Beneficial effects on the inflammatory reaction and the edema were seen by the end of two days. About 60 per cent of the patients complained of a moderate degree of pain at the site of the injection. The pain disappeared within 24 hours after treatment was stopped. In patients with granulating wounds, healing was hastened by the reduction of the surrounding edema. Delayed healing was not observed. Ten per cent of the patients showed a rise in temperature attributable to the streptokinase. Significant change in the white blood cell count, the differential count or prothrombin times was not seen. Fibrinolysis by the whole-blood technic was not observed in periods up to 72 hours, after the fifth injection of streptokinase on the third day of treatment. Hemorrhage and the formation of hematomas or petechiae were not seen.

In 64 patients with various types of inflammation, the results were excellent in 45, good in 15 and poor in four. In the poor results, the

blood supply was poor in three patients and sufficient treatment was not given to one.

It is presumed that the liquefaction of thrombi of fibrin in arteries improves the local circulation. This permits delivery of greater amounts of oxygen to the involved area. Fibrinolysis in veins and lymphatics produces a more efficient circulation resorption of edema fluid. With the paths of delivery more widely opened, phagocytes, humoral antibodies and antibacterial drugs can reach the bacteria in greater concentration and act more effectively. The rearrangement of the physical and chemical environments may permit closer contact of these substances with the bacteria.

To obtain good results with the intramuscular injection of streptokinase, the involved area must have a good circulation. The antibacterial drugs must be given concurrently since one limiting barrier is being removed.

Where necrosis of tissue has occurred and an abscess has formed, incision and provision for drainage must be made. The local application of Varidase and TRYPTAR® is valuable in that they (1) liquefy viscous barriers, permitting more efficient action by the antibiotics and easier removal of the debris; (2) stimulate the appearance of normal leukocytes which can move freely to undertake phagocytosis, and (3) promote the growth of granulation tissue.

The ideal enzyme for débridement in abscess should fill a number of requirements. These cannot be satisfied by one enzyme, so that a battery of enzymes is perhaps the answer. The ideal enzyme would meet the following specifications:

1. Digests fibrin, pus and necrotic tissue.
2. Possesses a high coefficient of chemical activity.
3. Does not change in reaction.
4. Is stable.
5. Is effective in pH range of 4 to 8 with best action at pH 7.
6. Is not toxic or antigenic.
7. Does not cross the membrane of the living cell.
8. Is not inhibited by digestive products.
9. Facilitates antibacterial action.
10. Promotes repair.
11. Does not lose its strength in aqueous solution.
12. Is easily made.
13. Is easily used.
14. Is cheap.

The requirements for effective treatment of abscess by an enzyme are as follows:

1. Incision must be done and provision for adequate drainage made. The enzymes promote drainage by thinning thick material.
2. Slough must be removed from the wound surgically since the enzymes will not dissolve such tissue.
3. Foreign bodies must be removed from the wound.
4. The blood supply to the area must be adequate.
5. The enzymes must be placed in direct contact with their substrates in the area treated.
6. Treatment should be on a continuous rather than an intermittent basis.
7. The systemic use of the chemotherapeutic or the antibiotic agents is indicated.
8. The products of digestion must be removed effectively and frequently.

The fundamental principle in application is that the enzymes must make effective contact with pus to achieve lysis. The method will vary according to the anatomic site treated. In an abscess, two No. 18 Fr. urethral catheters may be placed into the cavity and a nylon pack inserted loosely. The solution of enzymes is injected through one of the catheters. After a period of four hours to permit digestion, mild suction is applied to the second catheter by a Stedman pump. In infections on a flat surface, the enzymes may be incorporated in LUBAFAX® or in carboxymethylcellulose jelly, both of which are soluble in water.

Varidase contains streptokinase and streptodornase. Streptokinase, considered previously, causes liquefaction of fibrin and prevents the conversion of fibrinogen to fibrin. Streptokinase is antigenic, and an antistreptokinase will be found in human beings as a result of its use. Streptodornase, which is essentially a group of depolymerases and requires activation by the magnesium or manganese ion, digests desoxyribonucleoprotein and desoxyribonucleic acid in pus. Lysis of these com-

pounds yields phosphoric acid, desoxyribose, purines and pyrimidines, a result similar to that achieved by acid hydrolysis.[45] Streptodornase is also antigenic.

Varidase is furnished in ampules containing 100,000 units of streptokinase and 25,000 units of streptodornase. The enzymes may be dissolved in 10 to 20 cc. of physiologic saline for use as a solution or mixed in 5 cc. of physiologic saline and suspended in 30 cc. of Lubafax or carboxymethylcellulose. The amount of solution or ointment used and the frequency of application will depend on the severity of the infection.

Tryptar, which is mammalian crystalline trypsin, digests fibrin, fibrinogen, albumin and globulin. The point of attack on the proteins in pus, excluding fibrin, is at a much lower level than occurs with streptodornase. Trypsin is a weak collagenase and mucinase.

Trypsin is available in ampules containing 0.25 gm. The enzyme may be dissolved in 10 cc. of Sorensen's phosphate buffer solution or dissolved in 5 cc. of Sorensen's phosphate buffer solution and suspended in 30 cc. of Lubafax. The amount of solution or ointment used and the frequency of application will depend on the severity of the infection.

The toxic effects from the topical application of Varidase and Tryptar are practically negligible. Use of the enzymes in closed spaces such as the pleural cavity may produce an elevation of temperature which will readily respond to the administration of antipyretics. Minor headaches and aching have been encountered when the enzymes were used in closed spaces. Prothrombin times have not shown a significant deviation from normal. Hematomas and areas of ecchymosis have not been seen. Allergic manifestations have not been encountered.

The bacteria present do not interfere with the action of Varidase and Tryptar. Infections due to all of the common bacteria and those due to the gas-forming anaerobics, tubercle bacilli, *Blastomyces dermatitidis*, *Actinomyces bovis* and *Histoplasma capsulatum* have been treated successfully.

Since enzymes have not been discovered for digestion of many of the harmful substances in pus, they must be removed mechanically from deep wounds. Air-vent suction employing two No. 18 Fr. urethral catheters and a Stedman pump is the most efficient way of doing this.

Summary

The biochemical approach to the problem of infection will help to achieve better treatment of the patient. Knowledge of the chemistry of wound infection at present is not advanced enough to recognize all of the factors which may be either helpful or harmful. The metabolites in the wound determine whether or not bacteria will survive and multiply to produce necrosis of tissue. The use of the proteolytic enzymes enables partial modification of the physical and chemical environments to obtain better therapeutic results. The administration of streptokinase intramuscularly in combination with the antibacterial drugs has produced a reversal of inflammation and edema in patients. Varidase and Tryptar, in addition, can be used locally wherever clotted blood, fibrin or pus is present following trauma or inflammation. If an abscess is present and incision and provision for drainage are made, streptokinase may be given intramuscularly for its systemic effect and Varidase may be applied locally. The proteolytic enzymes permit more efficient action of the humoral forces and the antibacterial drugs by removing the barriers about the bacteria. The use of the enzymes must be guided by sound surgical principles.

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Postgraduate Clinical NOTES

43. BREATH-HOLDING ATTACKS

Breath-holding attacks are important not only because of the worry which they occasion to parents but because of their resemblance to epilepsy. They usually start in the first 18 months of life. They can begin as soon as the first week, but are almost unknown after the age of four years. The attacks are usually brought on by anger, thwarting, punishment, an attempt to force the child to do something against his will, or to prevent him doing something which he has set his heart on. They may result from another child snatching a much-wanted toy from him. What is not commonly recognized is that attacks may be due to pain from a fall or injury, or to sudden fear.

British Medical Journal, August 1955, pp. 422-23

Surgical Rehabilitation of the Hand With Ulnar Palsy

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IN both peace and war, injury of the ulnar nerve is one of the most common peripheral nerve injuries. This is a crippling injury and almost always requires one or more reconstructive procedures. If the correct operation is performed at the correct time, the results are most rewarding.

MILTON T. EDGERTON

Many physicians seeing these hands still fail to advise their patients of the marked improvements possible with surgery, or of the importance of having this work carried out while the small joints of the hand are still mobile. If delay is permitted, faulty substitution movements become established as habits, and late trophic changes and fibrous contractures of the paralyzed muscles will make reconstruction much more difficult.

No one operation or series of operations will be the procedure of choice in the care of all lesions of the ulnar nerve. The level of injury, the number of associated structures injured, and the time lapse after injury are three of the most important factors to consider.

Level of Injury

Injuries in the upper arm or proximal forearm should be treated as early as possible with careful nerve anastomosis. Here there is a preponderance of motor fibers within the nerve, and experience has led us to expect very satisfactory return of function in the large forearm muscles. The sensation in the forearm and hand will usually return to a moderate extent, but this may require 18 to 24 months after neurorrhaphy at the elbow. Our experience with motor recovery of the intrinsic musculature of the hand has been disappointing in proximal nerve lesions. These small muscles tend to become fibrotic and contracted in spite of physiotherapy and electrostimulation of the muscle fibers. If motor nerve fibers ultimately reach these muscles, it is not evidenced by adequate strength and amplitude of movement in joints of thumb and fingers.

A striking exception to this is seen in cases

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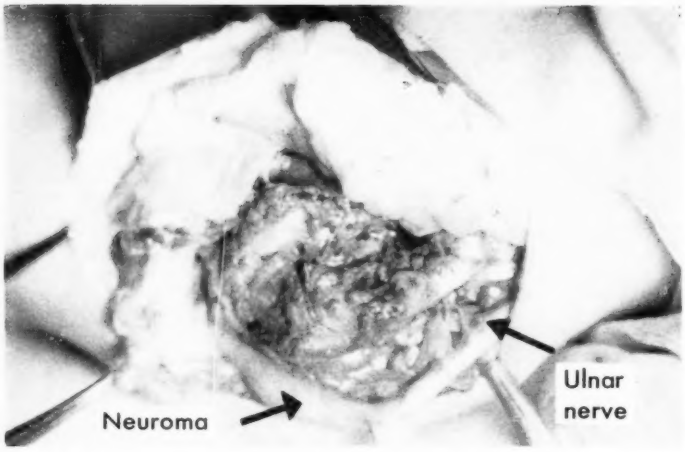

FIGURE 1a. Incision over medial aspect of elbow reveals neuroma in ulnar nerve at site of old supracondylar fracture. Complete motor and sensory paralysis appeared 18 years after fracture.

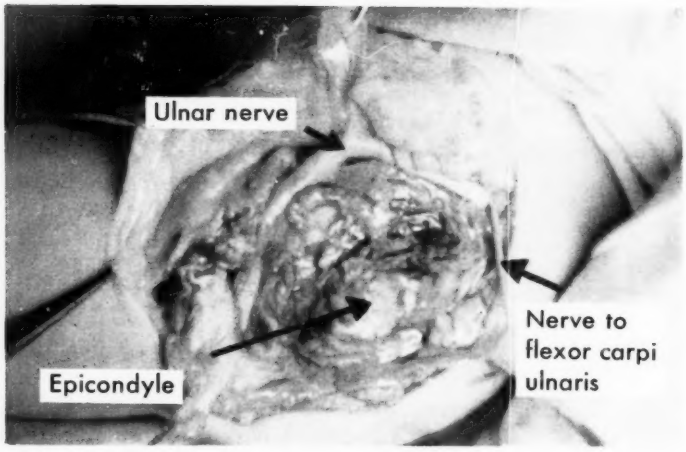

FIGURE 1b. Transplantation of the nerve to a subcutaneous position was not followed by recovery of function until the neuroma was resected at a second operation. Following this, a rapid return of sensation developed, but motor palsy remained.

of ulnar palsy due to chronic trauma at the elbow. Here arthritic changes or a callus from an old fracture of the humeral epicondyle may, by attrition, result in both sensory and motor palsy of the ulnar nerve distal to that point. If this condition is treated surgically before atrophy of the hand and forearm becomes manifest, the recovery of both sensation and motor power will be excellent. Late cases show recovery of sensation only. The treatment of choice is the mobilization and translocation of the ulnar nerve from the epicondylian groove to a new position anterior to the elbow. In doing this, care should be taken to bluntly separate the branches of the flexor carpi ulnaris and the flexor digitorum profundus of the little and ring fingers. These branches are allowed to remain in the original groove.[1] If the palsy is complete and a marked neuroma is present, the latter also should be resected and a neurorrhaphy performed (figure 1a, b). It is now established that the cell nucleus in the spinal cord shows definite changes after peripheral injury, and these changes seem to persist as long as the axons continue to regenerate and remain unsatisfied.[2]

Tinel's sign offers the earliest reliable evidence that the nerve is regenerating below the

point of anastomosis, but it is highly unreliable as to the ultimate completeness or quality of recovery. It should be stressed that one is not justified in waiting long months with the vain hope that the ulnar nerve will regenerate sufficiently to spare the patient future surgery on his unbalanced hand. The only case in which we have seen this regeneration occur was in a patient whose ulnar nerve was cut in the palm after the motor and sensory branches had separated. In this instance, nerve suture of the purely motor deep branch was followed by a pleasing recovery of intrinsic muscle function (figure 2a, b).

Time Lapse After Injury

Immediate repair—If the wound is clean and the patient can be treated within three to four hours after injury, gentle débridement should be done and all divided forearm and wrist tendons should be sutured. Any injured nerve or nerves should be sutured. In the case of skin loss, a split-skin graft or abdominal flap should be applied as an emergency proce-

FIGURE 2a. Meat-cleaver injury of hand with multiple divisions of extensor tendons. Deep motor branch of ulnar nerve was divided between fourth and fifth metacarpals.

FIGURE 2b. The motor branch of the ulnar nerve was repaired primarily and the extensor tendons were sutured. The badly damaged little finger was removed. One year later patient had 80 per cent recovery of use of intrinsic muscles, and full extension and flexion of fingers.

FIGURE 3a. This hand was injured at the wrist, and both ulnar and median nerves were divided along with the long flexor tendons to fingers and thumb. The nerves and tendons were all sutured on the night of injury.

FIGURE 3b. Early reconstruction of the intrinsic palsy was carried out eight weeks after injury, using the sublimis tendons that were repaired at the time of injury. One sublimis tendon was used to restore thumb opposition. Elastic splinting was used for two weeks.

FIGURE 3c. The tendon transfers were threaded through the lumbrical canals and attached to the intrinsic-extensor complex in each finger. The metacarpophalangeal joints were never allowed to go into hyperextension. Full, active extension resulted.

FIGURE 3d. Excellent strength and hand balance were obtained with only the emergency repair and one operation for tendon transfer. Three years later there was good return of sensation in all finger tips, but atrophy of intrinsic muscles was still apparent.

dure. With ulnar or median nerve injuries, we attempt to preserve and suture any divided sublimis tendons that may be used later for tendon transfers (figure 3). Immediate extensive tendon transfers or grafts are not justified at the time of this primary repair.[3]

Early repair—If primary skin healing is obtained by closure, graft or flap, and if no inflammatory changes develop, the hand is given a brief course of physiotherapy. As soon as any primary tendon and nerve sutures have healed, the motor and sensory loss of the hand is evaluated. In cases of ulnar nerve division at the wrist or above, there are many advantages in proceeding promptly with tendon transfers to replace the lost function of the intrinsic muscles. The interphalangeal joints are thus not allowed to stiffen in flexion, the metacarpophalangeal joints do not go into hyperextension, the collateral ligaments do not have time to shorten, splinting devices are not needed, and the entire course of morbidity is shortened for the patient.

Hands thus treated are still supple but lack the ability to flex metacarpophalangeal joints while extending interphalangeal joints. The index finger does not abduct against the thumb in a strong pinch, and the adductor pollicis will not fix the thumb and stabilize its base when the metacarpophalangeal joint of the thumb is in extension. Abduction of the little finger is lost but this usually is not important

to the patient, and opposition of the thumb usually is adequate unless there is an associated median nerve injury.

These early repairs usually are performed six to eight weeks after injury. One may use a variation of the Bunnell procedure to replace lumbrical function.[4] The sublimis tendon of the index finger is withdrawn in the palm and threaded through the second lumbrical canal to emerge on the ulnodorsal aspect of the index finger. Here the tendon is inserted into the intrinsic extensor complex near the lateral band. This not only gives metacarpophalangeal flexion, but it prevents hyperextension of that joint and thus permits the long extensors of the fingers to completely extend the interphalangeal joints. By attaching the sublimis tendon on the ulnar side of the dorsal hood, we provide adduction power to the index finger and rely on another transfer for abduction.

The sublimis tendon of the long finger is withdrawn in the palm and its two main divisions are split to that level. The two slips are then threaded through the lumbrical canals and attached to the radial aspect of each intrinsic extensor complex in the long and ring fingers, respectively.

The little finger sublimis tendon is quite tiny and is threaded as a single strand through the fourth lumbrical canal and attached with steel wire to the dorsoradial aspect of the extensor hood in the little finger. All four sublimis tendons usually are innervated by the median nerve.

The ring finger sublimis tendon thus is available for possible use in restoring opposition to the thumb in case the median nerve also was severed at the time of injury. Otherwise it may be used to restore adduction to the thumb. In restoring thumb adduction, the sublimis tendon is split back to the proximal palm and a single overhand knot is then placed, using the two ends of the tendon. This prevents subsequent separation of the fibers. One end is then carried across the palm and inserted into the ulnar side of the extensor complex of the little finger. The other slip is inserted into the adductor pollicis tendon. This not only provides thumb adduction but also restores useful palmar cupping and gives some degree of rotation and interphalangeal extension to the little finger.

For some years, I transferred the extensor indicis proprius into the first dorsal interosseous tendon in order to give abduction pinch to the index finger (figure 4), but recently we have used Littler's method which consists of transferring the extensor pollicis brevis into the first interosseous tendon.[5] The direction of pull is better, and more independent movement has resulted. When the extensor pollicis brevis is small, one of the sublimis tendons may be rerouted dorsally to the thumb metacarpal and attached to the first interosseous tendon to produce excellent index finger abduction.

Late repair—With late ulnar nerve lesions, additional and more complex problems arise. It is in this group of cases that we see the typical clawhand or *main en griffe*. The late effects of an unbalanced hand are clearly seen. The long tendons, or extrinsics, have continued to work. The metacarpophalangeal joints normally are flexed, almost exclusively, by the now paralyzed intrinsic muscles. As a result, the long extensors carry these joints into extension. The automatically tightened long flexors then pull the interphalangeal and wrist joints into flexion. The hyperextension position of the metacarpophalangeal joints deprives the long extensors of the power to extend the interphalangeal joints. Very soon the capsule of the metacarpophalangeal joint tightens and this joint can no longer be flexed, even passively. Subsequently, the capsules of the interphalangeal joints become contracted in a flexed position and the paralyzed lumbrical muscles become permanently overstretched.

Similar changes occur in the thumb region. The thenar arch is lost and the thumb becomes flattened. With disuse or an associated median nerve injury (figures 3 and 4), a severe adduction contracture may develop and prevent proper grasp. At earlier stages this may be overcome by elastic traction, but later it may necessitate resection of the adductor pollicis, first dorsal interosseous, and part of the flexor pollicis brevis. In very late cases, it may even be necessary to supply additional skin to re-create the thumb web.

FIGURE 4a. Arm caught in conveyor belt with avulsion of forearm skin, muscles, ulnar and median nerves, and muscle bellies of ulnar portion of forearm. Compound fractures of ulna made resurfacing urgent. An abdominal flap has been raised and is ready to apply.

FIGURE 4b. Undelayed abdominal flap is applied to promote surface healing.

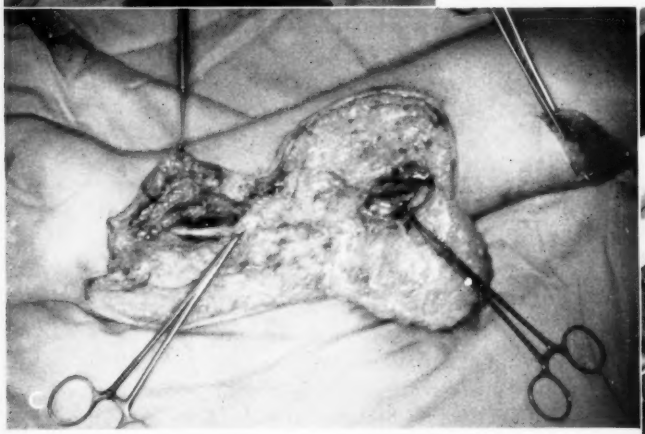

FIGURE 4c, d. At time of detachment the ulnar nerve was transplanted anteriorly to elbow and a 4 in. gap in the nerve was thus easily overcome.

FIGURE 4e. Wrist extensors and extensor indicis proprius were employed to give tenodeses to metacarpophalangeal joints and to supply power to long flexors of fingers, extension to thumb, and abduction to index finger. Excellent pinch and grasp now present without resorting to wrist arthrodesis. Proximal thumb joint is still unstable and may need a replacement for adductor.

Late sensory and trophic changes also appear a few months after injury. These add greatly to functional impairment and complicate treatment. The most noticeable are (1) tapering of the fingers and distressing atrophy of digital pulps, (2) striation of nails and alterations in hair growth, (3) loss of sweating, (4) atrophy of skin rugae and loss of surface friction, and (5) diffuse stiffening of joints.

Approximately 3 per cent of patients will develop causalgia after ulnar nerve injury. This is not to be confused with the neuralgia due to a neuroma at the site of injury. The neuralgia may respond temporarily to a dorsal sympathectomy, but if long continued it is unlikely to improve until the scarred neuroma is resected.

Essentially, the patient with a complete, untreated ulnar nerve palsy of six months' duration has only three motor functions of value with his clawed hand. He has a static hook in his flexed fingers; he has limited opposition because of the hyperextended metacarpophalangeal joints; and he has some interdigital pinch, largely as a result of the action of the long extensor and flexor tendons. Varying amounts of joint contracture have developed. How may he best be helped surgically?

Selection of Operation

If not previously performed, nerve suture can be of value in late cases to restore sensation and to overcome trophic changes (figure 4). We have seen sensation return after an interval of 10 years between injury and nerve suture.

The status of joint mobility in the hand and wrist must be assessed. If the joints can be moved passively, the metacarpophalangeal joints should be stabilized in slight flexion, and if the patient can then voluntarily completely extend the interphalangeal joints one may utilize the modified sublimis tendon transfers as described under "Early Repair." However, if these lesions are long standing, we have found, as pointed out by Riordan,[6] that many patients develop a set habit of flexing the wrist when they wish to extend their fingers. This habit persists even after surgery and, of course, tends to relax the sublimis transfers and prevent them from stabilizing the metacarpophalangeal joints. For this reason we have tended to use a tenodesis for late cases of ulnar palsy. The tenodeses described by Fowler[7] and Riordan[6] both continue to act in the presence of wrist flexion and have served nicely in these late cases.

In Fowler's procedure,[7] the extensor indicis proprius and extensor digitorum quinti minimus are each detached from their insertions and split into two parts. One of these four slips is then passed through each interosseous space to enter the lumbrical canal and pass anteriorly to the transverse metacarpal ligament. These tendons are then inserted into the intrinsic-extensor complex. We tend to tighten these tendons somewhat more than Fowler suggested, because we find that they should hold the metacarpophalangeal joints in approximately 80 degrees of flexion when the wrist is held in the neutral position. Only one slip is passed to each finger, and it is placed on the radial side. The constant effect of gravity on the fingers in the usual carrying position of the human arm tends to cause a tendency to some ulnar deviation of the fingers. This force apparently counterbalances the radial attachment of these tenodeses, as we have seen no late radial deviations. It is evident that there is no active gliding of these extensor tendons through the interosseous spaces, but they do tend to limit wrist flexion somewhat and thus help overcome wrist flexion deformities.

Riordan[6] has suggested a reflection of long tendinous strips from the extensor carpi radialis longus and extensor carpi ulnaris. These strips are left attached distally at the metacarpals, and the free ends are split and threaded through the interosseous spaces after the manner of Fowler.

These tenodeses are based on our realization that extension of the phalanges is carried out by both the intrinsic muscles of the hand and the long extensors. Duchenne's[8] original idea that the long extensor tendons could not extend the distal phalanges can be shown to be wrong simply by holding the metacarpophalangeal joints in slight flexion with an ulnar palsy and noting that the long extensor tendon completely extends the phalanges. In

fact, one occasionally will see a late case of ulnar palsy that has not developed clawing because of incidental contracture of the volar portion of the capsule of the metacarpophalangeal joint. In this fashion, a spontaneous stabilization of the metacarpophalangeal joint has occurred and the long extensors can continue to give full extension to the fingers.

In the event that the patient cannot extend his phalanges with the metacarpophalangeal joint stabilized, three possible situations may exist: (1) It may be possible to extend the phalanges passively; (2) it may not be possible to extend the phalanges passively until after several months' use of a gentle elastic extension splint, or (3) it may not be possible to extend the phalanges passively, even after splinting, because of permanent contracture of the volar joint capsules.

In the first two instances, two sublimis tendons can be removed from the finger and each split into four strands. Two of these strands can be used in each finger. They are routed along the lumbrical canals, over the lateral aspects of the extensor hood, and then cross one another over the dorsal apex of the proximal interphalangeal joints (figure 3). Here they are attached in order to extend the proximal phalangeal joints to within 25 degrees of full extension. This will not only permit the finger tips to oppose the thumb pulp once more, but will also allow the long extensor to act more strongly on the distal phalangeal joints. This tenodesis is usually under considerable tension, and great care must be taken to hold the wrist and metacarpophalangeal joints in marked flexion for five weeks after surgery.

In cases where permanent joint damage prevents positioning by tenodesis, one should resort unhesitatingly to a combination of capsulectomy and arthrodesis. Capsulectomy is most useful in the hand when applied to the metacarpophalangeal joints of the fingers and occasionally the thumb. The older procedure of bilaterally removing windows of the thickened and shortened collateral ligaments is dangerous. If the excision is excessive the long extensor tendon may drift ulnarward, resulting in serious crippling of the hand. The limited excision of only the ulnar collateral ligament and careful stripping of the volar plate usually will give adequate joint flexion. If this is not sufficient, one occasionally may find it necessary to resect the metacarpal heads and to arthrodese the joints in functional flexion. This also tends to relax the long flexors somewhat and permit better grasp.

Arthrodesis of the proximal interphalangeal joints is commonly necessary in late cases. If continuous gentle elastic traction will not bring these joints beyond 90 degrees of extension, a fusion is indicated. We have found 30 degrees of flexion gives a good pulp-to-pulp pinch with the thumb and also allows the long flexors to exert their full power on the metacarpophalangeal and distal phalangeal joints. The fingers then permit a graceful, strong grasp. Without this arthrodesis, intrinsic palsy causes the fingers to curl up on themselves before flexing on the palm.

At times the distal phalanges may be so atrophic and contracted that simple amputations of the tips will give both a better working surface and a better contact with the thumb pulp. In general, a full-length finger requires more mobility than a shortened one for useful function.

With long-standing clawhand, the thumb may also become contracted so as to lose its web. This is, of course, even more marked if the median nerve is also paralyzed and opposition is lost. The tiny abductor pollicis brevis is needed to stabilize the thumb metacarpophalangeal joint in a position of flexion, abduction and slight pronation. This not only positions the thumb for strong grasp, but aids in the extension of the distal joint of the thumb. If this muscle is paralyzed, the thumb metacarpophalangeal joint goes into hyperextension and the extensor pollicis longus is unable to extend the distal thumb joint. A ring sublimis may be transferred around the flexor carpi ulnaris tendon as a pulley, and then attached into the tendon insertion of the abductor pollicis longus. This gives excellent opposition when the thumb is still passively mobile. At times it will be necessary simultaneously to perform a tendolysis of the extensor pollicis longus when performing this transfer for opposition. If so, as Brand[9] and others[5, 10] have

shown, it is usually best to open the carpal tunnel and place the extensor pollicis longus in a subcutaneous position.

At times, one must surgically excise the fibrotic adductor pollicis and first dorsal interosseous muscles and insert an iliac bone graft between the first and second metacarpals. Care should be taken to rotate the first metacarpal strongly medialward before fixing the graft. This procedure is sometimes of value in a more pliable hand if paralysis is quite extensive and if very few active tendons remain for transfer.

Arthrodesis of the wrist is of great value when motor paralysis is so extensive that the wrist flexors and extensors are needed for the more critical movements of the fingers and thumb. We have found it most helpful with repair of hands after poliomyelitis, cerebrovascular accidents and cervical paraplegia.

New and improved prosthetic devices are being developed for use in cases of more extensive paralysis. In general these are more helpful if they are designed to leave exposed any finger tips that still have sensation. By and large, they supplement but do not replace surgical rehabilitation of the hand.

Results and Summary

This report deals with personal experiences in the treatment of 46 cases of ulnar palsy between 1947 and 1954.*

The etiology of the palsy in these 46 cases was: (a) trauma, 35 cases; (b) poliomyelitis, 6 cases; (c) cord tumor, 2 cases; (d) muscular dystrophy, 1 case; (e) syringomyelia, 1 case, and (f) leprosy, 1 case.

Five of the lesions represented partial losses of ulnar nerve function. The remainder were complete. Twenty-two of the patients whose condition was due to trauma and two in whom it followed removal of cord tumors were seen within the first two months after onset of palsy. In these 24 patients, all but two obtained excellent results following reconstructive procedures on the nerves, skin, tendons and bones of the hands (figures 2, 3 and 4). The average number of operative procedures required was 1.8 per patient, and only two arthrodeses of joints were necessary.

In contrast, the group of 22 patients seen after a lapse of more than two months required an average of 3.2 operations each. 17 arthrodeses were required, and even then only 12 of the 22 ended up with hands that were as functionally satisfactory as those of the group receiving early surgery. In addition to ultimate functional loss, the late cases required weeks of complicated splinting and months of morbidity before returning to work.

The striking difference in prognosis between those receiving early and those receiving late surgery was one of the most impressive features of our follow-up. Physicians in general are not aware that the hand of a patient with ulnar palsy should be reconstructed as soon after injury as feasible. Much can be done at the time of the original injury to pave the way for a good ultimate result.[3]

Several changes occur in a hand in the first few months following injury that are difficult to correct later.

Early tendon transfers will serve as built-in, constantly active, dynamic splinting.

Early nerve repair may head off trophic changes and give prompt return of sensation.

Delayed repair of the tendinous mechanism leads to changes that make the job much more difficult for both surgeon and patient.

*These patients were treated in conjunction with Dr. Anthony Zovickian, Dr. Stanley Hoffmeister and Dr. John D. DesPrez while they were associated with the Plastic Service at The Johns Hopkins Hospital.

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Actinomycosis: Some Concepts of Therapy and Prognosis

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DESPITE the fact that strains of *Actinomyces* are highly sensitive to antibiotics, the disease caused by these microorganisms continues to present difficult therapeutic problems. The type of tissue reaction is fairly characteristic, and offers the most logical explanation for some of these problems. The involved areas are usually quite extensive, markedly indurated and relatively avascular in the region of the growing organisms. Thus it is easy to understand the difficulties presented, first of all in getting a bactericidal concentration of drug into the areas of active infection, and second in attempting to restore the involved tissues to as nearly a normal state as possible. These facts serve to emphasize two general principles in therapy, namely, the necessity of surgical drainage or even excision in many cases, and the need for intensive, prolonged medical therapy.

The organisms causing most of the infections in humans are the *A. bovis*, which can be recovered in most cases from the lesions or exudate, and often are found—in the absence of infection—on the gums, in the crypts of tonsils and, perhaps, on other mucous membranes. They are gram-positive, branching, filamentous organisms, and are strictly anaerobic in their growth. Their isolation is best carried out on Brewer's thioglycollate medium, or on plates of blood agar, under anaerobic conditions. Growth usually appears on primary isolation in from two to four days, but is likely to be more rapid on subculture.

The lesions of actinomycosis—whether in animals or man—are subacute or chronic, and

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usually progressive in character. The involved tissues become swollen and indurated, with relatively little tendency to suppurate. One characteristic of the infection is the formation of multiple draining fistulas. In many cases, at one stage or another during the course of the infection, sulfur granules may be demonstrated, thus making the diagnosis more certain. When examined microscopically, the granules are found to be round or irregular, and to consist of a dense reticulum of gram-positive filaments which are often arranged radially and which may have small clublike endings.

The lesions of actinomycosis tend to spread mainly by contiguity. As a result, large areas of the skin and subcutaneous tissues frequently are involved. According to Conant and Rosebury,[1] the disease is of the cervicofacial type in more than half of the cases in which it occurs in man. It apparently originates in the mouth and spreads in the usual way through the soft tissues, and occasionally even involves the bones. These authors said that the disease involves the thorax in about 15 per cent of cases, and the abdomen in about 20 per cent.

In the abdomen, the most frequent site is the region of the appendix or cecum. From there, the infection may spread to the abdominal wall and form an indurated mass which suppurates and may form fistulas. At times, the infection spreads to the liver and causes localized abscesses. In rare instances, it evidently invades the blood stream, which might account for the brain abscesses or meningitis which is present in some cases.

In reviewing some of the literature relating to the therapy of actinomycosis, one is impressed by several points that seem worthy of emphasis. For instance, prior to the sulfonamide era, there were no drugs which were capable regularly of influencing the infection favorably, although potassium iodide often seemed to exert an inhibitory effect. Dramatic improvement was found to occur with administration of sulfonamides, and later with penicillin.[1-5] Later reports of interest brought out the necessity of large doses of penicillin and sulfonamides for prolonged periods,[6] and considered the value of the broad-spectrum antibiotics in this condition.[7-9] The fundamental need for surgical therapy in combination with these drugs, in cases of actinomycosis, is a point that has been stressed in nearly all the reports on the subject.

We have analyzed the records of 36 cases of actinomycosis in which the patients were treated at the Johns Hopkins Hospital in the past 25 years. In many of the cases in which the patients were observed in the early part of this period, the records and data were somewhat incomplete, but in cases in which the patients were observed more recently the records were adequate for more detailed study. Eighteen of the 36 patients are known to have recovered; 14 patients either have died or have not obtained any improvement.

Table 1 shows the site of the lesions in the 36 cases. On reviewing the data in this table, one is impressed at once with the high incidence of abdominal lesions as compared with those in the cervicofacial region. Of the 91

TABLE 1

SITE OF LESIONS IN 36 CASES OF ACTINOMYCOSIS

SITE OF LESIONS*	NUMBER OF LESIONS
Cervicofacial region	
Neck	4
Jaw	3
Mastoid bone	2
Other portions	3
Thorax	
Lungs	10
Pleura	6
Thoracic wall	5
Abdomen	
Abdominal wall	15
Intra-abdominal abscess	8
Pelvic organs	6
Colon	6
Subphrenic abscess	4
Cecum	4
Liver	4
Stomach	3
Other regions	
Brain	3
Retroperitoneal region	3
Blood stream	2

*Of the 91 lesions that were present in the 36 cases, 50 (54.9 per cent) involved the abdominal wall or abdominal viscera, 21 (23.1 per cent) involved the thoracic wall or thoracic viscera, and 12 (13.2 per cent) were situated in the cervicofacial region.

lesions that were present in these cases, 50 (54.9 per cent) involved the abdominal wall or abdominal viscera, and 12 (13.2 per cent) were situated in the cervicofacial region. This is at distinct variance with the statement often made in the literature, and referred to earlier, namely, that the disease is of the cervicofacial type in more than 50 per cent of the cases.

The most logical explanation for this apparent discrepancy is that the diagnosis is made more often in cases of the cervicofacial type because the clinical picture of this type of infection has been better established and the infected area is more accessible; whereas, in the case of abdominal actinomycosis—unless the abdominal wall itself is involved—the lesions are more difficult to reach for biopsy or culture. Because of this, it seems likely that the abdominal type more often may go undiagnosed unless the presence of the condition is suspected much more frequently, and unless careful cultures and sections are made in every case. It likewise should be pointed out that repeated smears and cultures usually must be made and that many sections must be made of any biopsy or autopsy material before a definite diagnosis can be reached.

There are other points brought out by the table which may be worth emphasizing. For instance, although the appendix and cecum are recognized as common sites of primary infection, other parts of the colon would seem to be implicated much less frequently. However, in four of our patients the transverse colon was the site of extensive lesions. An additional occurrence of considerable interest was the finding, in two of these four cases, of a fish bone buried in the inflammatory tissue, and apparently responsible for perforation of the colon which had taken place in each. Foreign bodies frequently are thought to play a role in the cervicofacial type, and these findings make it interesting to speculate on their probable importance in the development of actinomycosis in other areas as well.

The stomach is another organ that is rarely involved in this process—at least to be recognized as a primary site—and yet in three of our cases the infection may well have had its origin there, for in each case there was a perforation with abscess formation. In four cases, the spread of the infection from some abdominal focus to the subphrenic space was not such an unusual development. It is, however, well worth considering when dealing with the difficult problem of abscesses in this region. In two cases, the chief site of infection was in the mastoid bone. In one of these cases, the patient currently is undergoing treatment. He was thought preoperatively—mainly on the basis of x-rays—to have a malignant lesion. At operation, the mastoid bone was found to be destroyed by a peculiar sort of inflammatory tissue from which an anaerobic *Actinomyces* was cultured. This man is now doing well following an extensive operation combined with antibiotic therapy.

Differential Diagnosis

In view of many of the factors already considered, it is not hard to understand the difficulty in diagnosis in many cases of actinomycosis. Tuberculosis, whether in the lungs or in other organs, may be impossible to differentiate without careful and repeated examination of exudates or of tissues removed at operation. The same holds true for pyogenic infections, particularly those due to staphylococci, which often run subacute or chronic courses and may produce the same type of lesion. Another error commonly made is the diagnosis of a malignant tumor; this was true in five of the cases in this series. This diagnosis may be based on the clinical appearance of the lesions or on the roentgenologic findings, and it even may be made at operation when the involved tissues are found to be quite firm with little evidence of suppuration. It is obvious, therefore, that one should consider this condition much more often than we usually do, and no matter what parts of the body are involved.

Treatment

The course in many of our cases, as well as in cases reported by others, suggests that best results will be obtained by the proper combination of medical and surgical therapy. Sometimes surgical drainage may be all that is necessary, but, in many cases, extensive

excision of involved tissues also should be carried out. Potassium iodide may be of value in an occasional case if given in doses as large as tolerated. Sulfonamides are definitely inhibitory to *Actinomyces* and may have a place in combination with antibiotics.

Pathogenic strains of *Actinomyces* have been found to be sensitive to most antibiotics, but there has been a much wider experience with penicillin than with the others, and it stands at present as the antibiotic of choice. One reason for this choice is that large doses can be given for long periods; other reasons are that it penetrates tissues well and has a bactericidal action. Other antibiotics are being employed now with good results,[7-10] but a long period of observation will be necessary in order to make a final estimate of their worth. It is our feeling that, in the majority of cases in which the lesions are extensive, large doses of penicillin—3,000,000 to 6,000,000 units per day—should be given for six months or even longer. Such long-term therapy of actinomycosis, which is aimed at complete eradication of the infection, follows the general principles of treatment for tuberculosis, a disease which it resembles in many ways.

Summary

This report is based primarily on an analysis of the records of 36 cases of actinomycosis treated at the Johns Hopkins Hospital during the past 25 years. Of the 91 lesions that were present in these cases, 50 (54.9 per cent) involved the abdominal wall or abdominal viscera, 21 (23.1 per cent) involved the thoracic wall or thoracic viscera, and 12 (13.2 per cent) were situated in the cervicofacial region. In 18 of the 32 cases in which adequate follow-up data were available, the patients had recovered; in the remaining 14 cases, the patients either were unimproved or had died.

The clinical picture is exceedingly variable. The disease frequently is confused with tuberculosis, with other chronic infections or with malignant tumors. Careful and repeated cultural and histologic studies are necessary to make the diagnosis in most cases.

The therapeutic regimen should include surgical drainage, and extensive excision when indicated by the character of the lesions. The most effective medical therapy seems to be the administration of large doses of penicillin, which at times should be combined with the sulfonamides or with one of the other antibiotics. These agents should be administered for a prolonged period.

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Therapeutic Emotional Interactions in Group Treatment

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A RATIONAL approach to psychotherapy may be based on the premise that functional mental illnesses are in part expressions of distress engendered by the patient's disturbed relationships with others, and of his self-defeating efforts to cope with this distress. The goal of psychotherapy is to help him overcome these faulty modes of adjustment and to develop more successful ones.

The central process of psychotherapy, as we see it, is the challenge of the appropriateness of the patient's maladaptive responses under conditions which help him to give them up and develop better ones. This requires that the therapeutic situation stimulate or elicit the faulty response, to help the patient to perceive it for what it is, to find alternative ways of responding and to facilitate the generalization of the successful ones to everyday life. The therapeutic situation, finally, must support and strengthen the patient's self-esteem. Without such support he will not have the courage to examine what he is doing or to experiment with alternatives.

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Psychotherapy must involve the patient's emotions if it is to succeed, as these supply the motive power to disrupt habitual response patterns and the incentive to find better ones.[1] Modification of attitudes in therapy is usually gradual and fluctuating, but there are occasional episodes of concentrated emotional impact which seem to accelerate the change as well as consolidate earlier gains. In group therapy these episodes are often produced by interchanges among patients, as well as between a patient and the therapist. The purpose of this paper is to report two therapeutic emotional interactions between patients in a therapy group, to cast light on how this form of treatment operates.

These groups consist of five to eight patients, meeting once a week for an hour and a half. Although the examples are taken from a group consisting only of women with a male therapist, mixed groups are the rule. Members usually encompass a wide range of diagnoses, but are within the spectrum of neurotic or mild psychotic disturbances. The procedure is that of free, informal discussion. There is no agenda, and the doctor exerts leadership indirectly through the kind of behavior he encourages or discourages, and the nature of his interpretative comments, rather than through direct guidance.

Early meetings of these groups are apt to be uneasy affairs. The patients are strangers to one another. Many feel self-conscious about revealing their need for psychotherapy in front of others. All are uncertain as to how to proceed and may fear that they will be called on to reveal intimate personal problems. They see the group leader (who is usually a physician) as the sole source of help and therefore compete with each other for his attention. This situation rapidly elicits patients' habitual ways of coping with stress. They resort to the usual social technics of getting to know one another, search for superficial similarities in symptoms or experiences, and offer carefully selected and edited items of personal history. Neurotic behavior patterns soon emerge, as patients compete for the doctor's interest. Some, by relentlessly complaining, seem to be declaring that they suffer the most and therefore most need him. Others by assuming an exaggerated air of competence and superiority seem to be trying to prove that they are most deserving of his attention. During this period, while accepting these and other behaviors, the doctor tries constantly to reinforce those trends which make for a therapeutic group atmosphere, that is, one in which everyone's contributions are taken seriously and free emotional expression is encouraged provided the patient assumes responsibility for trying to understand why he feels as he does. The doctor encourages interaction among the members, which gradually results in a decrease of their efforts to seek his individual attention.

In an established group patients have come to see themselves as being helped by the group *and* the doctor rather than by the doctor in spite of the group. As they develop confidence that their real selves will be accepted, patients are better able to tolerate tension, which appears higher than in early meetings because feelings are expressed more bluntly. During this phase the chief function of the doctor, who is much less active, is to help patients examine the attitudes revealed by their interactions.

In relation to the psychotherapeutic process, the emotionally charged, intimate atmosphere of a mature therapy group readily elicits patients' maladaptive as well as healthy interpersonal responses. The life experience and group behavior of the other patients offer to each one a variety of alternatives to his own neurotic behavior. Their honest expression of their reactions helps them to become clearly aware of what they do, and guides them as they experiment with other ways of responding. By its similarity to real life situations, the group facilitates the carry-over of what is learned in it to everyday living.

How the therapeutic group strengthens the self-esteem of its members may not be obvious, especially since neurotics often feel contempt for themselves and therefore for each other, and are encouraged to express their feelings without too much regard for the sensitivities of the person to whom they are directed. In early meetings lack of support may indeed be a problem and may cause some patients to drop out of the group. A mature group, however, supports the self-esteem of its members in many ways. Demoralizing feelings of isolation are combated by the discovery that they have problems or symptoms in common. Patients, usually to their surprise, find that they can give as well as receive help. The group atmosphere, with its relative absence of pressure to conformity and its air of seriousness, conveys to each member that his feelings are worthy of respect. A patient may even experience a strong attack as supportive if he perceives it as evidence that he is being taken seriously, and if the attack is seen to be aimed not at him as a person but at a neurotic aspect of his behavior, with the implication that the

attackers know that he can do better.

Group therapy has an advantage over individual therapy for certain patients in that they can directly experience in a therapeutic setting how their neurotic behavior affects others. This has more emotional impact, hence a greater therapeutic potential, than merely reporting such experiences from daily life to the doctor. Moreover, group members offer a wider range of possible alternative behaviors than does a single therapist. They may serve as models more successfully than the doctor, because patients often see him as too different from themselves to be a useful guide.

Once a group is well established, the relative lack of privacy does not prevent most patients from expressing feelings freely and discussing intimate problems. Contrary to our initial apprehensions, fear of gossip outside the group, or its actual occurrence, has seldom been a problem. It appears that reticence toward outsiders becomes part of the group code.

The following two examples of therapeutic emotional interchanges in the same therapy group, involving the same two patients at different times, may serve to bring the therapeutic processes of these groups into sharper focus. They illustrate two common types of interaction. In the first, a patient is prevented from carrying out a habitual neurotic reaction and at the same time is presented with a better alternative which she later adopts.* In the second, the group stimulates a patient to behave as she had always wished but feared to do because of imagined disastrous consequences. When disaster does not in fact follow such behavior, when experimentally tried in the group, the new behavior pattern is strengthened.†

The group consisted of six housewives with neurotic difficulties. Two were phobic, two obsessive and two hypochondriac. Though all complained at length of their symptoms in individual interviews preparatory to joining the group, they did not do so in the early group sessions. The meetings soon became very lively, with much interaction among the members and free expression of feelings toward each other and the male therapist.

The two hypochondriac patients, whom we may call Mrs. Jones and Mrs. Smith, were the ones primarily involved in these episodes. Mrs. Jones was a 44 year old housewife who complained of headaches, abdominal pain and periods of uncontrollable irritability and depression of several years' duration. Her difficulties developed in the setting of a tense relationship with a gambling and emotionally unresponsive husband, and with her oldest daughter whom she characterized as "sassy and unconcerned" about her. The patient had marked exacerbation of her symptoms when involved in her frequent arguments with this daughter. Although she seemed aware of her interpersonal difficulties, Mrs. Jones seemed to expect medicine to give her relief and expressed doubt that "talking things out" would help. She showed no understanding of the possible relationship between her symptoms and personal difficulties.

Mrs. Smith was a 32 year old housewife who complained of nervousness, gagging and fullness in the stomach. She connected her symptoms directly with her mother, a demanding, complaining woman who, the patient felt, favored her younger sister. The mother brought all her complaints to the patient, asked her advice, then rejected it. She expressed strongly ambivalent feelings toward her mother: "I love her so much, I resent what she is doing." She could not tell her mother how she felt and was ashamed of her attitude. Her stomach cramps and jittery feelings came on when she felt anger at her mother and was unable to express it. She often had anxiety attacks when her mother criticized her. Her general attitude seemed to be "You must not show your feelings or people will take advantage of you."

In the group Mrs. Smith frequently spoke of her problems with her mother. Without fail Mrs. Jones reacted by becoming angry and accusing Mrs. Smith of being ungrateful. She would then proceed to defend mothers including herself by stating that all children were unappreciative. Mrs. Jones' sensitiveness caused some other members to exercise self-restraint in criticizing their mothers, but not Mrs. Smith.

*For a comparable case see Powdermaker and Frank.[2]

†For comparable cases see Frank and Ascher.[3]

who apparently was unable to control her intense feelings toward her mother.

The seventeenth meeting was attended by five members. It started out with expression of hostility toward doctors in general and the group leader in particular who had just returned from an extended vacation. Mrs. Smith took the lead in this, but when she began losing support from other group members she shifted to her favorite topic, criticism of her mother. Mrs. Jones, exceptionally calm at first, defended her position in relation to her daughter after another patient suggested that she might resent her daughter's independence. A third member joined in the conversation by referring to a sermon given by her minister in which he had stressed the importance of mother love for a child in addition to providing the necessities of life. This seemed to be the last straw for Mrs. Jones who had managed to control her mounting tension up to that point. She suddenly jumped to her feet, gasped, said she felt weak and ran toward the door, shouting that she could not stay as long as mothers were being discussed. Mrs. Smith quickly rose, ran after Mrs. Jones and with her arm around her begged her to stay. The rest of the group joined her in pleading with Mrs. Jones to sit down. This she did but moved her chair away from the group and continued to say that she would have to leave. When the doctor asked her what she was upset about she replied that she could not take the talk about mothers any longer. She again expressed the desire to leave but when urged by the doctor to remain and "face it," she moved her chair closer to the group, assisted by Mrs. Smith.

The group continued the discussion about mothers and seemed concerned about helping Mrs. Jones to understand what had precipitated her acute upset. When one of the other patients suggested that Mrs. Jones looked on Mrs. Smith as if she were her own daughter, she admitted having thought so herself and having made a remark to her husband to that effect. She also accepted the interpretation by the group that she felt guilty toward her daughter and that this feeling had caused her defensiveness. Mrs. Jones calmed down considerably for the remainder of the session. Upon leaving, one member remarked that this was "the best thing that could have happened to Mrs. Jones." Everyone in the group, including the doctor, shared this opinion.

During subsequent meetings, Mrs. Jones' attitude showed a striking change. She seemed more comfortable and felt more a part of the group. She no longer showed explosiveness and was more inclined to examine events and attitudes that might be at the basis of whatever emotions she experienced. Even though her feelings toward Mrs. Smith (and her daughter) were changed, the conflict was by no means resolved (e.g., some months later she vigorously denied that it was Mrs. Smith who had led her back to her chair during that crucial session). Yet her headaches became infrequent and she did not take medicine for them but tried instead to examine the underlying emotional tensions.

By reminding Mrs. Jones of her conflicts concerning her daughter, the group elicited her habitual neurotic response, an emotional outburst, but the consequences were not those she had come to expect. Mrs. Smith, who represented her daughter, instead of responding in a "sassy" fashion showed genuine concern. At the same time, the group refused to be intimidated by her display and continued with their serious discussion of mothers. This set Mrs. Jones the example of dealing with disturbed feelings by trying to discover their sources and meanings. Thus the group demonstrated to her the inappropriateness of her neurotic response and suggested a better alternative. At the same time they offered her the support she needed to stick to this experience and profit from it.

Mrs. Smith's therapeutic emotional experience occurred many months later. She participated actively in the group from the start, at first in a superficial way. After the episode previously related she became clearly aware that she was identifying Mrs. Jones with her mother, an identification which was strengthened when Mrs. Jones later denied that it was Mrs. Smith who had helped her. Mrs. Smith was very resentful toward Mrs. Jones for her "lack of appreciation" but could not tell her so. At the same time she continued wanting to

help her, thus practically duplicating her attitudes toward her mother.

In the course of the next few months Mrs. Smith's symptoms improved. Her feelings toward her mother had eased to the extent that "I don't get sick when she makes the same old nuisance of herself," yet she still could not express her resentment. She took the lead in focusing the group discussion on sexual difficulties, over the protests of Mrs. Jones.

The day before the seventy-second meeting (in the nineteenth month of treatment), Mrs. Jones called Mrs. Smith and told her she wasn't coming to the group because she (Mrs. Smith) talked about sex all the time. In reporting this to the group, Mrs. Smith said Mrs. Jones was acting exactly like her mother, and that she had felt frightened and resentful after the telephone conversation. She added that she still felt extremely guilty and could only talk this way because Mrs. Jones was absent. Scarcely had these words left her lips when Mrs. Jones walked in, looking deeply distressed. She wore no make-up, her hair was stringy, and, as she collapsed in her chair, she seemed about to weep. Mrs. Smith's tension visibly mounted until suddenly she burst into tears and began screaming hysterically: "I caused it, I know it's my fault! I caused it, I caused it, I know it's my fault!"

At this point in order to reduce the almost unbearable tension the doctor asked Mrs. Smith why she felt as she did. Mrs. Smith said: "It's the way I feel about my mother. I know I caused her to feel the way she does." Mrs. Jones listened carefully and then said calmly: "What makes you think *you* caused this? It's something entirely different." She then described some recent temper outbursts against her husband and son, then resentment at her husband for his indifference. Her self-analysis contrasted sharply with her earlier behavior. While she spoke Mrs. Smith brightened up more and more as she came to see that her assumption of responsibility for Mrs. Jones' upset was entirely baseless. At the following meeting, Mrs. Smith said she felt a good deal better after having discovered that Mrs. Jones had not been mad at her but was upset at something else. The next week she indicated that she no longer felt obligated to listen to her mother's complaints or give in to her demands.

It was not until two months later that Mrs. Smith was able to criticize Mrs. Jones to her face. She did so by laughingly telling Mrs. Jones, who was complaining, that she was just trying to make everyone feel bad because she was feeling bad. Some weeks later the doctor noted: "Mrs. Smith can take Mrs. Jones much better and there is a good deal of warm exchange between the two."

In this example Mrs. Smith, under the impact of her group experiences, gradually became less fearful of and guilty toward Mrs. Jones who represented her mother, until finally she was able to defy her openly by continuing to discuss details of her sexual difficulties. Mrs. Jones' emotional upset seemed to confirm her worst fears, but this was immediately followed by the startling discovery that Mrs. Jones was really disturbed about something quite unconnected with Mrs. Smith. This experience, which helped Mrs. Smith to see that her feelings were not as destructive to others as she had feared, was followed by her increasingly direct criticism of Mrs. Jones, followed by a much better relationship between them. Concomitantly, the gaining of emotional independence from her mother was increased.

Summary

Psychotherapy aims at modification of noxious interpersonal attitudes. This occurs as the result of clarification of inappropriate responses and provision of possible alternatives, accompanied by opportunity for testing them while protecting or even enhancing the patients' self-esteem. Two examples are presented to illustrate how therapeutic groups, through the kind of emotional stimuli they provide, can be especially effective in bringing about such modifications.

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Hazards of Blood Transfusion

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THE earliest recorded blood transfusions were from animal to man, and were followed by severe and often fatal reactions. Transfusions of human blood were rarely attempted, and even when successfully completed were often accompanied by unpleasant reactions. The discovery of human blood groups by Landsteiner and the development of the science of preserving and storing blood for indirect transfusion have increased the safety and facility with which transfusions can be administered and have brought about an enormous increase in their use. The great majority of these transfusions proceed with no untoward effects because of the development of better technics in handling blood and insuring immunologic compatibility. Despite this, serious transfusion reactions still occur and their incidence is high enough to make transfusions inadvisable except where a valid need exists.

Mechanical Factors

Transfusion reactions may occur for a variety of reasons. Mechanical factors can account for troublesome and even fatal complications. When blood is infused rapidly, signs and symptoms of pulmonary edema may develop, especially if underlying heart disease existed before the transfusion. The rate and amount of blood transfused should be carefully regulated to prevent pulmonary edema. Certain patients will benefit if the supernatant plasma is removed, and the red blood cells then may be administered in a smaller volume. If pulmonary edema occurs, phlebotomy should be done to decrease circulating volume.

A more serious mechanical error that may occur when blood is being "pumped" is air embolus. Prevention of this complication is

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important, for air embolism is often fatal. It can occur when the method for rapidly infusing blood depends on increasing the air pressure in the blood container through the venting needle. If this method is used, one specific person should be responsible for a single bottle and have no other duties to distract him. This precaution is necessary, for in a few seconds, when the blood has been emptied from the container, enough air can enter the patient's circulation to prove rapidly fatal. Other methods of rapid infusion, such as a rotary pump acting on the tubing or direct pressure on plastic bags as blood containers, are less dangerous.

Hypersensitivity Reactions

A variety of symptoms can develop in the recipient of a transfusion due to some reaction of an allergic nature with material in the donor blood. The simplest and most frequent occurs soon after the transfusion has been started. The patient may complain of itching, and then urticaria and angioneurotic edema may develop. There may be some rise in temperature. These reactions, although troublesome, are seldom serious. They are self-limited, but if the patient is uncomfortable the symptoms often can be relieved by the administration of epinephrine or an antihistaminic. Some patients who receive repeated transfusions will manifest these allergic phenomena repeatedly. It may be wise in such cases to administer an antihistaminic just prior to or at the same time as the transfusion. This will often prevent the allergic reaction.

Some hypersensitivity reactions can be more severe. In an occasional patient, severe bronchospasm will develop. A delayed reaction sometimes is encountered, manifested by continued fever, joint pains and swelling and severe malaise. Rales may develop in the lungs, and x-rays taken after transfusion show areas of opacity. These clear rapidly and are probably best explained as "pulmonary hives." When these more serious hypersensitivity reactions occur, antihistaminics and epinephrine may not be of value, and the administration of cortisone or hydrocortisone can be of great help to the patient.

Reactions Caused by Agents Accidentally Transmitted During Transfusion

A number of diseases can be transmitted from donor to recipient via blood transfusion. Malaria, relapsing fever, syphilis and several other infectious diseases theoretically are capable of being passed to the recipient, but these situations rarely occur in this environment. The prevention of their transmission is accomplished by careful screening of donors and by performing serologic tests for syphilis. It has been shown that even blood of known syphilitic donors is rendered safe for transfusion purposes by storage for 96 hours.[1]

A more serious and common problem is the transmission of hepatitis. This disease, caused by the transmission of a virus from the blood of the donor to the recipient, occurs with relentless mathematical regularity. A study carried out at the Johns Hopkins Hospital[2] showed that one of every 330 patients transfused returned to the hospital with clinical evidence of hepatitis. Unquestionably the true incidence was higher, since some patients in whom hepatitis developed did not return to the hospital. In this same series, 11 deaths occurred among 40 patients with hepatitis. If there were no other complications of blood transfusion except homologous serum jaundice, this problem alone would warrant a cautious, conservative attitude on the physician's part in ordering blood transfusions.

Another serious type of reaction occurs following transfusion of blood that has been contaminated with bacteria.[3] The organisms that cause this type of reaction have the ability to grow at 4° C.,[4] and the severe reaction produced probably results from the accumulated endotoxin. The clinical syndrome that ensues following infusion of contaminated blood is often so characteristic that the diagnosis can be suspected before bacteriologic confirmation is obtained. The reaction generally begins with a shaking chill and a rise in temperature. This is followed by abdominal pain, nausea and vomiting, and diarrhea. Severe hypotension follows which persists and becomes the most difficult therapeutic problem. The diagnosis can be confirmed by examining some of

the blood from the bottle or transfusion tubing for bacteria. Cultures should be obtained but treatment must be started immediately if the patient is to have any hope of survival. Therapy should include broad-spectrum antibiotics, norepinephrine and corticoids.

A similar mechanism is responsible for the less serious but more common pyrogenic reactions. These are due to the presence of sterile bacterial products in the anticoagulant solution or in the transfusion equipment. Better technics of pyrogen testing and the use of disposable transfusion equipment have reduced the number of these reactions.

Reactions Caused by Immunologic Phenomena

Despite improved technics for typing and crossmatching blood, hemolytic transfusion reactions continue to occur. The majority are due to mechanical errors in labeling or transcription or even administering blood to the wrong patients. Crossmatching procedures using protein media and the indirect Coombs technic have helped greatly in eliminating hemolytic transfusion reactions due to unusual antibodies in the recipient. Prevention of these reactions must therefore include a system of "checks" and "double checks" to eliminate mislabeling and misdirecting the blood for transfusion, and technical procedures capable of detecting antibodies in all the clinically important blood group systems.

When a patient receives incompatible blood, the clinical picture can vary from little or no change to a rapidly fatal reaction. A typical moderately severe reaction starts with malaise, restlessness and perhaps headache and backache. A shaking chill and a rise in temperature follow. There may be some abdominal symptoms and hypotension but not of the same order as in reactions following transfusion of contaminated blood. Sometimes a hemorrhagic diathesis becomes apparent.[5,6] This is especially important in the anesthetized surgical patient where the earlier signs are masked. Therefore, the onset of unexplained generalized bleeding during surgery should make the surgeon suspicious if a transfusion is in progress or has just been completed. Hemolytic transfusion reactions are confirmed by demonstrating hemoglobinemia and hemoglobinuria and by re-examining the blood types and crossmatching.

If the patient survives the initial insult there is almost invariably some renal damage, and proper management of the acute renal failure can save the patient's life. The

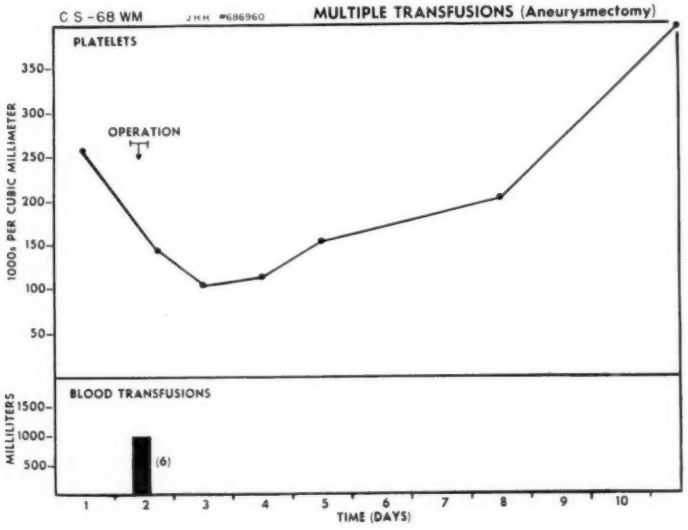

FIGURE 1. The patient was a 68 year old white man who received 3000 ml. of whole blood during the surgical removal of an aneurysm of the abdominal aorta.

conservative therapy suggested by Bull and associates[7] in 1949 has given better results than most other methods of treatment.

Another type of reaction which may be due to immunologic mechanisms is the "plasma transfusion reaction." This is seen more commonly in patients who require repeated transfusions over a long period. It is characterized by a febrile reaction and a failure to demonstrate the expected increase in number of red blood cells. These reactions can be ameliorated or prevented by removing the plasma and washing the red blood cells prior to transfusion. In some cases the administration of corticoid compounds before transfusion is also necessary to prevent reaction.

Reactions Due to Unknown Mechanisms

Recently, attention has been called to a hemorrhagic diathesis that occurs following the rapid transfusion of large quantities of blood,[8, 10] even though immunologic incompatibility cannot be demonstrated (figure 1). The hemorrhagic diathesis is mainly due to thrombocytopenia. The fall in the platelet count is proportional to the amount of blood transfused and to the rate of transfusion.[10] Since these patients may continue to bleed, they require additional transfusions, and a therapeutic dilemma is reached where the additional transfusions may accelerate the abnormal bleeding.

Conclusions

Whole blood transfusions are a valuable aid in the management of elective surgery and play an irreplaceable role in the treatment of medical and surgical hemorrhagic catastrophes. However, the physician must realize that each transfusion is accompanied by the hazard of an untoward reaction. These reactions may result in increased morbidity or death. Therefore, the physician should pause and decide whether the particular indication for blood transfusion justifies this risk. Often a re-examination of the problem will reveal another therapeutic path—more circuitous perhaps, but safer.

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MEETINGS *and Postgraduate Courses*

University of Minnesota, Minneapolis: Continuation course in cancer detection for general physicians, February 16-18, at the Center for Continuation Study, under the direction of Drs. O. H. Wangensteen, Professor and Chairman, Department of Surgery, and W. A. Sullivan, Director, Cancer Detection Center.

University of Minnesota, Minneapolis: Continuation course in recent advances in internal medicine for internists, February 13-15, at the Center for Continuation Study, under the direction of Dr. C. J. Watson, Professor and Head, Department of Medicine. Dr. Joseph W. Jailer, Associate Professor, Department of Medicine, College of Physicians and Surgeons, Columbia University, will be the guest speaker.

University of Minnesota, Minneapolis: Continuation course in eye, ear, nose and throat for general physicians, February 27-29, at the Center for Continuation Study, under the direction of Dr. L. R. Boies, Clinical Professor and Head of the Department of Otolaryngology, and Dr. Erling W. Hansen, Clinical Professor and Head of the Department of Ophthalmology.

Interstitial Hernia: A Problem in Diagnosis

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INTERSTITIAL hernia does not follow one of the usual pathways of abdominal hernias but lies in between any of the various layers of the abdominal wall. According to Watson,[1] this type of hernia was first observed by Bartholin in 1661. Erdman[2] states that it generally occurs in the male and is frequently associated with maldescent of the testicle; the hernial sac, unable to pass out of the inguinal canal, spreads out in some other direction.

Lower and Hicken[3] were able to collect 587 cases of the various types of interstitial hernia from the literature in 1931. They added two cases of their own. In spite of this, the condition is still so rare as to present a diagnostic problem unless a hernial mass can readily be demonstrated. Lower and Hicken stressed the difficulty of preoperative diagnosis.

Apparently the first case of interstitial hernia in a woman was described by Velpeau[4] in 1841. Luke[5] in 1850 reported two more cases. Golding-Bird[6] reported two cases in 1884, and Berger[7] three cases in 1891. In 1900 Auvray[8] reported a case and collected 13 others from the literature. However, the condition is relatively rare in the female. Lower and Hicken state that it occurs 3.5 times more frequently in men.

Another case of interstitial hernia in a woman is herein reported, one which presented considerable diagnostic difficulty.

Case Report

A 25 year old married woman was first seen by me on December 13, 1951. Five years previously she had had two stones in her right kidney, which she had passed. About a year later she had the same sort of pain. She went to Dr. Richard W. TeLinde, who did a thorough urologic examination and found nothing

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wrong with her kidney—no stones, no ptosis, no ureteral stricture and no evidence of any genitourinary pathologic condition. Since then she had had pain off and on in each inguinal region, but worse on the right. The pain occurred at least once a month but was not related to her menstrual periods. The pain had become progressively more frequent and severe. She had been seen by a good many physicians and had recently had a thorough diagnostic check up in which no abnormality was found. On the night of December 8 she had noticed a lump in her right inguinal region, and the night before I saw her she had noticed one in the left inguinal region. She went to see Dr. Ernest H. Gaither, who thought that she had a hernia and sent her to me.

Physical examination—The external inguinal rings could not be palpated on either side and there was no impulse on coughing in those areas. There was no evidence of femoral hernia. A defect could be felt in the region of the internal inguinal ring on each side, and on the right side there was an impulse on coughing. Just mesial to the internal inguinal ring on the right, there was a slightly tender mass about the size of a hazelnut which was not reducible.

Impression—I felt that the patient had an inguinal hernia on each side but I could not be sure of it. I had her return a few days later for further observation. At the time of the second examination the situation was unchanged, except that the mass and impulse on the right were more definite than they had been at the time of first examination. Operation was therefore advised.

The patient entered the Union Memorial Hospital on December 26, 1951. There still was no change in her condition, except that the mass on the right side had become slightly larger. It covered an area about the size of a quarter and felt irregular, as if it might have omentum in it. Due to the fact that the patient had had so many examinations with negative findings, a member of her family requested a consultation, which was readily granted. Dr. Harvey B. Stone was the consultant. He concurred in my findings and felt that the patient should be operated on.

Operation—The next day (December 27)

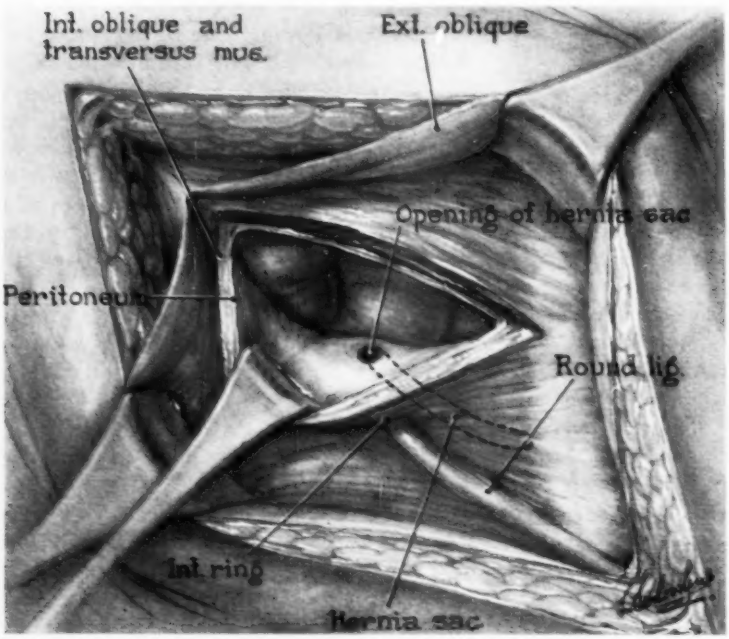

FIGURE 1. The lower border of the LaRoque incision has been retracted in order to show the opening into the hernial sac, which did not follow the round ligament as usual, but extended mesially between the muscles.

the patient was operated on under PENTOTHAL® sodium, nitrous oxide and oxygen, with curare. A right inguinal incision was made and the canal opened. The round ligament was thoroughly explored and no evidence of a hernial sac found. A LaRoque[9] muscle-splitting incision was then made about an inch above the internal ring and the abdominal cavity opened. With a finger in the peritoneal cavity, it was found that the floor of the inguinal canal was very firm and solid, and no evidence of hernia could be made out, either femoral or inguinal. The abdominal wall forming the lower border of the muscle-splitting incision was then elevated with a small appendix retractor and the peritoneal surface in the region of the internal ring inspected (figure 1). Immediately a small opening was seen, which was only 3 or 4 mm. in diameter. A Kelly clamp could be introduced into this opening for about two inches. This was obviously the hernial sac. However, it did not follow the round ligament, but extended out into the muscles mesial to the round ligament. The fundus of the sac was grasped with a Kelly clamp and brought up into the peritoneal cavity. It was loculated and surrounded by scar tissue, so it was freed with some difficulty. It was transfixed, ligated and excised, this procedure taking place within the peritoneal cavity. The small opening in the transversalis fascia was closed with interrupted sutures of black silk. As the floor of the inguinal canal was solid throughout, no further plastic operation was done. The aponeurosis of the external oblique was closed with medium black silk, interrupted; the subcutaneous tissue with fine black silk, interrupted; and the skin with fine black silk, continuous.

A left inguinal incision was then made and the inguinal canal opened. Again, no hernial sac was found in connection with the round ligament. A LaRoque incision was again made and again no hernial sac could be palpated with a finger in the abdominal cavity. However, on inspecting the parietal peritoneum in the region of the internal ring, the same type of opening was found as that found on the right side, and the sac was of the same nature except that it was only about half as long as that on the right. It was dealt with in exactly the same manner and the wound closed as on the other side.

Postoperative course—The patient's convalescence was entirely uneventful and she was discharged from the hospital on the twelfth postoperative day.

She has been examined at frequent intervals since operation, the last examination being on January 17, 1955. She has had no more inguinal pain and the operative sites have remained firm.

Comment

It is generally easy to demonstrate the presence of a hernia. However, that is not always the case. Every experienced surgeon has seen cases in which he could not demonstrate a hernia at one time, but could at other times. When there is a definite history strongly suggestive of hernia, it is much better to say that the patient may have a hernia but it cannot be demonstrated at the present time, than to say flatly that he or she does not have a hernia. Interstitial hernias are much harder to diagnose than ordinary hernias. The case reported here caused the patient a good deal of inconvenience, and the presence of a hernia was hard to demonstrate, it having been missed by a number of able clinicians.

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Factors Which Influence the Results of Mitral Commissurotomy

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NUMEROUS reports in the literature[1-3] in recent years testify to the fact that relief of mitral stenosis by a direct surgical attack on the diseased valve can be carried out with a reasonably low mortality and with benefit to a majority of the patients selected for operation. In a consecutive series of 150 operations for mitral stenosis performed by Dr. Alfred Blalock and his staff at the Johns Hopkins Hospital from November 1949 to June 1954, the operative mortality has been 7.3 per cent, and 71 per cent of the patients have been improved to some extent after operation. Table 1 summarizes the present status of these 150 patients, who have now been followed for periods varying from six months to five years.

We have classified as "greatly improved" those patients who are now virtually free of the symptoms which troubled them before operation and who require little or no restriction of activity at present. Seventy-nine patients showed such a degree of improvement, and most of these at present belong in Functional Class I of the New York State Heart Association classification.[4] Twenty-eight patients are moderately improved in that their symptoms have diminished and their exercise tolerance is increased but their activity still must be restricted to some extent. Twenty-seven patients have not improved or have be-

TABLE 1

RESULTS IN 150 OPERATIONS FOR MITRAL STENOSIS

	NUMBER	PER CENT
Greatly improved	79	52
Moderately improved	28	19
Unimproved or worse	27	18
Deaths		
At operation or less than one week afterward	11	7
One week or more after operation	5	3

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come worse since operation. Sixteen patients have died, 11 at the time of operation or within seven days after operation, and five during the follow-up period.

Although these results are encouraging, the facts that the degree of improvement varies and that some patients are not helped or are made worse by operation emphasize the need to recognize the individual factors which determine whether a patient will benefit from mitral commissurotomy. When the cases summarized in table 1 were reviewed, several factors appeared to have a significant influence on the operative results.

1. Mitral Insufficiency

Severe mitral insufficiency had a clearly adverse effect on the results of operation. Of six patients with marked insufficiency, one was moderately improved after operation, three were unimproved or worse, and two have died.

A mild or moderate degree of mitral insufficiency, on the other hand, did not affect the results. Eighteen patients had a mild degree of insufficiency and five a moderate degree (as judged by the surgeon at the time of operation), in addition to a significant degree of stenosis. Of these 23 patients, 15 are greatly improved, four moderately improved, two unimproved and two dead, an over-all result not significantly different from that in the group as a whole.

Although these figures indicate the importance of estimating correctly the relative severity of stenosis and insufficiency of the mitral valve, this constitutes a difficult diagnostic problem. In nine of our cases the degree of mitral insufficiency was seriously underestimated before operation, including two patients who proved to have almost pure insufficiency.

Auscultation is the most useful single procedure in identifying the predominant mitral lesion. The typical diastolic murmur of mitral stenosis, occupying the latter two-thirds of diastole and best heard at or somewhat medial to the apex, is well known. A "mitral opening snap" in early diastole, and a late crescendo accentuation of the diastolic murmur are present in most but not all cases with predominant stenosis. A loud, snapping, apical first sound is an important sign and almost always indicates that mitral stenosis is the dominant lesion.

Apical systolic murmurs can be quite misleading, since they occur frequently in the absence of mitral regurgitation. In general, an apical systolic murmur with an intensity of grade 2 or less should not be regarded as evidence of mitral regurgitation in the absence of other signs.

Definite radiologic or electrocardiographic evidence of left ventricular enlargement is a good sign that mitral insufficiency, or at least some lesion other than mitral stenosis, is predominant, but unfortunately this evidence is lacking in some cases with marked regurgitation. Many special diagnostic methods for differentiating between stenosis and insufficiency have been suggested, including left auricular systolic expansion by fluoroscopy or roentgen kymography,[5] pressure tracings from the pulmonary arterial "wedged" position,[6,7] angiocardiography[8] and others, but in our hands none of these have proved reliable. In cases where the evidence from history, physical examination, radiography and electrocardiography indicates that both stenosis and insufficiency are present, and yet it is impossible to decide which is the predominant lesion, it is probably advisable to explore the valve surgically, in the hope that stenosis will prove to be the more important lesion and can be relieved.

2. Aortic Stenosis

Five patients had stenosis of both mitral and aortic valves. In two of these cases commissurotomy was performed on both valves. One patient has improved since operation; the other has not improved, and remains in chronic congestive failure. In three of the five cases mitral commissurotomy alone was carried out. Two of these patients died during or shortly after operation. The other survived and is moderately improved.

The combined operation, in which the mitral valve is reached through the left auricle and the aortic valve is approached by an instrument through the left ventricle, is a much more severe operation than mitral commis-

surotomy alone and has a mortality at present of about 20 per cent. In patients with significant stenosis of both aortic and mitral valves, such a combined procedure is the surgical treatment of choice, but we feel this operation should be reserved for patients who are very severely handicapped by their disease.

3. *Aortic Insufficiency*

We have not been willing to advise mitral commissurotomy in cases complicated by severe aortic insufficiency. Two patients with a mild degree of this lesion, however, have been operated on in this series. Both showed only minimal peripheral signs of aortic insufficiency, and the evidence indicated that mitral stenosis, with resulting strain on the right side of the heart, was the predominant abnormality. One patient is greatly improved and the other moderately so.

4. *Other Cardiac Lesions*

In five cases there was a history of severe, prolonged, right-sided heart-failure, with little response to intensive medical therapy. Two of these patients showed signs of tricuspid insufficiency, probably secondary to right ventricular dilation and failure, and neither showed any improvement after mitral valvotomy, although satisfactory widening of the mitral opening was accomplished at operation. Of the other three patients, one is moderately improved, one is worse, and one died during operation.

Two patients in this series of 150 operative cases proved to have no mitral stenosis or other valvular disease. One of these patients had the typical clinical findings of mitral stenosis, but at operation a congenital lesion of the left ventricle which produced a "submitral" stenosis was found. The other had a diffuse mediastinal scarring of unknown etiology which obstructed the pulmonary venous return to the left auricle. Both these cases have been described in detail elsewhere.[9]

5. *Embolism*

This is an important factor principally because it is responsible for a large part of the operative mortality. The incidence of embolism in this series, before and after operation, is shown in table 2. Both pulmonary and systemic emboli have been included.

Of the 19 patients with a definite history of emboli prior to operation, six (31 per cent) suffered another embolus either at the time of operation or within four days after operation. This is an incidence five times greater than in the group of 131 patients with no history of preoperative embolism, eight (6 per cent) of whom had emboli at operation or in the early postoperative period. Almost half (6 out of 14) of all operative and early postoperative emboli were fatal.

These figures must be considered in the light of the incidence of embolism in similar patients not subjected to surgery.[10] When a patient with rheumatic heart disease has had one embolus, the chance of subsequent hemiplegia or death from another embolus is so great that systemic embolism in a patient with mitral stenosis is in itself probably an indication for commissurotomy, even taking into account the greater operative risk in these patients. The available evidence, although still incomplete, strongly suggests that the inci-

TABLE 2

MORTALITY IN RELATION TO PREOPERATIVE EMBOLISM

PREOPERATIVE EMBOLI	NUMBER OF CASES	POSTOPERATIVE EMBOLI*	DEATHS		
			Embolic	*Other*	*Total*
Yes	19	6 (31%)	3 (16%)	0	3 (16%)
No	131	8 (6%)	3 (2%)	10 (8%)	13 (10%)
TOTAL	150	14 (9%)	6 (4%)	10 (7%)	16 (11%)

* All within four days postoperatively.

dence of embolism is decreased after mitral commissurotomy, once the early postoperative period is safely past. In our series only one significant systemic embolus has occurred during the follow-up period to date.

6. Auricular Fibrillation

Although auricular fibrillation usually develops late in the course of rheumatic heart disease, its presence did not prejudice the operative result in our series except for the frequent association of preoperative auricular fibrillation and embolism. Fifty-six of our patients had auricular fibrillation before operation, and 13 of these, or 23 per cent, had a definite history of embolism. This was an incidence four times higher than that in the group with normal rhythm, in which 6 out of 94 cases had emboli before operation. Excluding the effects of embolism, the results of operation in fibrillators and nonfibrillators were not significantly different.

7. Active Rheumatic Fever

Activity of the rheumatic process is usually regarded as a temporary contraindication to cardiac surgery. In eight of our cases, when signs of activity persisted after a long period of preoperative treatment, we eventually decided to proceed with commissurotomy. Five of these patients had an excellent result, one is moderately improved, and two died within four days after operation. The two fatalities occurred in patients who were seriously ill before operation and were known to be poor operative risks. One had multiple pulmonary emboli and died of a final major pulmonary embolus. In the six survivors, the preoperative signs of activity had consisted of persistent elevation of the sedimentation rate, mild fever and sometimes fleeting and migratory muscle pains in the shoulders or extremities. Such signs, in a patient who is well compensated and otherwise in good condition, do not absolutely contraindicate commissurotomy, although every effort should be made to suppress the rheumatic activity with salicylates or cortisone before surgery.

After mitral commissurotomy, a certain number of patients experience one or more attacks of an acute illness which may be recurrent rheumatic fever, coming on from two weeks to several years after operation. The characteristic features of these episodes are chest pain and fever, sometimes accompanied by arrhythmias, transient joint pains or psychoses. Such attacks, which have been termed the "post-commissurotomy syndrome,"[11] have appeared in 18 (12 per cent) of our patients from two weeks to four years after operation. In 13 cases these episodes have had no apparent adverse effect on the patient's subsequent course. In five cases, all with prolonged signs and symptoms, progressive cardiac failure has appeared and responded poorly to treatment, and two of these patients have died.

8. Pulmonary Hypertension

Long-standing mitral stenosis not only produces an elevation of the left atrial pressure by mechanical obstruction to flow, but also leads to an increase in pulmonary arteriolar resistance, and probably to anatomic pulmonary vascular changes.[12] In some cases with extremely high pulmonary arterial pressures these changes may be irreversible, and relief of the obstruction at the mitral valve may give only partial relief of the pulmonary hypertension. In our experience, however, it has been impossible to predict the extent to which pulmonary hypertension will be reduced by commissurotomy, and excellent results have been obtained in some of these patients, although the pulmonary artery pressure rarely returns to a completely normal level.[13] Of eight patients with pulmonary arterial pressures greater than 85 mm. Hg systolic or 45 mm. Hg diastolic, four are greatly improved, two are moderately improved and two are not improved.

Summary

These are some of the most common and important of the factors which influence the success or failure of mitral valve surgery. It should be noted that the age of the patient, within the limits of our observations, was not a significant factor. The oldest patient in this series was 56 years of age, and a total of 17 patients were more than 45 years old at the

time of operation. The results in this group are essentially the same as in our younger patients, which is in agreement with other reports.[14]

It seems clear that there are no *absolute* indications or contraindications for mitral commissurotomy. In each case the degree of disability and the complicating factors must be weighed against the chances of benefit from surgery. Among the factors which diminish the patient's chance of a good operative result are the presence of a marked degree of mitral insufficiency, a marked degree of aortic stenosis or insufficiency, a long history of right ventricular failure responding poorly to treatment, marked enlargement of the heart, and a definite history of embolism. In some cases mitral commissurotomy is indicated in spite of these complications, and offers the possibility of significant improvement.

Acknowledgments

The study of these patients before and after operation has been carried out jointly by the author and Dr. E. Cowles Andrus, Associate Professor of Medicine, Johns Hopkins University School of Medicine. We are deeply indebted to Dr. Alfred Blalock, Professor of Surgery and head of the Department of Surgery, to Dr. Henry Bahnson, Associate Professor of Surgery, and to the other members of the surgical staff who were responsible for the operative procedures and the surgical care of these patients. We are also grateful to the many members of the visiting staff and house staff of the Johns Hopkins Hospital who have made their patients available for study, and to the members of the Surgical Physiology Laboratory who performed the cardiac catheterization.

This work has been supported in part by a grant from the Maryland Heart Association.

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Postgraduate Clinical NOTES

44. DIFFERENTIAL DIAGNOSIS OF BREATH-HOLDING ATTACKS

Breath-holding attacks are often confused with epilepsy, but it is essential to distinguish the two. As the attacks are not often seen by the doctor, the diagnosis rests essentially on a careful history. The orderly and rather slow sequence of events in the breath-holding attacks, a few cries after a known precipitating factor, followed by breath-holding in expiration, the rapid onset of cyanosis, followed by limpness and convulsions in that order, differ from epilepsy, in which fits rarely follow any precipitating factor, though it should be noted that over-ventilation, as from excessive crying, can precipitate a fit in an epileptic. In epilepsy the so-called epileptic cry before a convulsion is unusual in children, and when it does occur it is usually different in nature from the child's ordinary cry.

British Medical Journal, August 1955, pp. 422-23

A Brief Review of Breast Physiology

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THE science of endocrinology has made tremendous advances in the past few decades, and in many instances laboratory findings have contributed materially to better understanding of clinical problems. Unfortunately, this is not completely true of breast lesions. The frequency of breast carcinoma has focused the attention of clinicians and the efforts of research physiologists on the underlying physiologic processes in an attempt to anticipate the abnormal. Breast tissue is not essential to life, yet it has been shown to be influenced by almost every hormone in the body; it reflects the endocrine pattern of a particular subject, so a knowledge of the hormonal changes is helpful in interpreting pathologic findings.

All endocrine function in the body is mediated through the pituitary gland, which in turn is influenced not only by the other endocrine glands and the general nutritional status but also through the nervous system, through the hypothalamus (figure 1). It is in the hypothalamus that neural stimuli are integrated with humoral factors, such as the blood levels of the various hormones. The hypothalamus is probably the site of the sympathetic and parasympathetic centers, and in addition plays an important part in regulating body temperature and energy exchange. The control of emotional states appears to originate in this area, and it has been observed that emotional disorders not infrequently are accompanied by disturbance of the genital functions, particularly the menstrual rhythm. It seems more than coincidental that a patient complaining of painful breasts will often be a thin nervous woman, often with a history of sterility. A further example of this linkage is the breast enlargement which may occur in pseudocyesis.

The Hypophysis or Pituitary Gland

The actual hormones responsible for changes in the ovaries and the breasts are those of the anterior pituitary. Pituitary deficiency has

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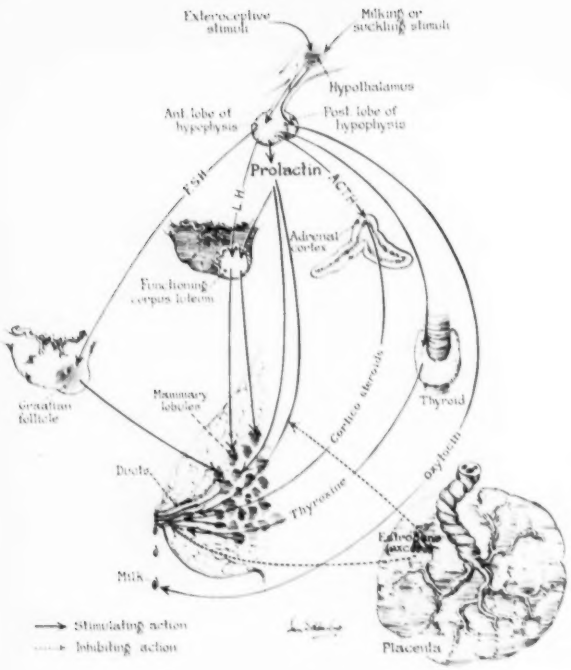

FIGURE 1. Hormonal relationships of the breast.

been found to lead to atrophy of the gonads and involution of the breasts. The pituitary produces two hormones, the prime function of which is to act on the gonads—the follicle-stimulating hormone (FSH), and the luteinizing or interstitial cell-stimulating hormone (LH or ICSH). These hormones are known as pituitary gonadotropins and are similar in nature to the chorionic gonadotropin of placental origin which is found in pregnancy urine and detected by biologic means to establish a diagnosis of pregnancy. In experimental animals the placenta is able to maintain mammary development following hypophysectomy.

Once puberty is reached, a rhythmic relationship is established between the pituitary and the target organs. The result of the release of FSH is to stimulate the growth of the ovarian follicle beyond the state of antrum formation. During this time LH also is being secreted, and when the LH:FSH ratio reaches a certain level, ovulation occurs with the formation of estrogen. The function of estrogen is to stimulate the continuing release of LH and to mobilize cholesterol in the ovary. Astwood[1] decided that the pituitary gonadotropins do not provide the full answer to the ovarian changes, and demonstrated that a third pituitary hormone, prolactin, is necessary to form progesterone from cholesterol.

Most observers agree that the gonadal hormones, estrogen and progesterone, are essential for breast development. However, Turner and his associates[2,3] have advanced the theory that gonadal hormones act only as pituitary stimulants—that a factor called mammogen I, produced in response to estrogens, leads to ductal development; and that mammogen II, stimulated by a combination of estrogen and progesterone, is responsible for lobular-alveolar growth. One fairly common clinical observation tends to contradict this theory: if estrogen is administered by local inunction, only the treated breast responds, instead of both, as would happen if the action were mediated by the pituitary.

The pituitary hormone which is regarded as the actual mammary growth stimulant is prolactin. Nelson[4] has suggested that the functions of prolactin are threefold—luteotropic, mammotropic and lactogenic—and vary with the needs of the body. Undoubtedly the role of prolactin in progesterone formation indirectly influences breast development, but Lyons[5] was able to prove that prolactin had a direct stimulating effect on mammary epithelium. During pregnancy the actual growth stimulus is provided by estrogen and progesterone, supplied in large quantities by the placenta. The mammary gland of pregnancy does have a special affinity for prolactin, but much less so than the lactating gland. It is possible that prolactin is responsible for the presence of secretion in the alveoli late in pregnancy.

Various theories have been advanced to explain the mechanism of converting milk secretion to milk production. A high level of circulating estrogens has been thought to inhibit both the release and local action of prolactin. However, a more logical view would appear to be that of Petersen,[6] who thinks that the stimulating factor is oxytocin, which is re-

leased by the posterior pituitary during parturition and which acts on the muscle fibers of the breast. So it would seem that prolactin, together with the other hormones of the anterior pituitary, is responsible for milk formation, and oxytocin for its ejection.

The Gonadal Hormones

There are three groups of gonadal hormones—estrogens, androgens and progesterone. All are steroid in nature and allied to cholesterol. Their function appears to be that of stimulating cell proliferation and differentiation in structures common to both sexes—the embryonic müllerian and wolffian apparatus, the nipples, breasts and external genitalia. Their action is organ rather than sex-specific. All three hormones are produced in both sexes, and it is possible that they may be converted from one to another in vivo, under abnormal circumstances.

The ovarian hormones are estrogen and progesterone, and both play a definite part in breast development. Mammary epithelium is unusually sensitive to hormone stimulation, though for the most part changes induced in the mature animal are reversible.

The breasts in infancy consist of simple branching ducts, and remain so until the endocrine changes of puberty bring a steady supply of estrogen. Then the area of arborescence gradually increases, and club-shaped swellings appear in the terminal ducts. Usually there is an increase also in the periductal stroma; this may become exaggerated in certain areas and lead to the formation of a fibroma or a fibroadenoma. Alveoli are not usually found until menstruation becomes ovulatory in character.

Opinions differ greatly on the breast changes accompanying the menstrual cycle. Loeb and Hesselberg[7] in 1917 drew attention to distinct phases in the mammary glands of guinea pigs as related to the sexual cycle. Since then observers have tried to find a similar pattern in human breast tissue. It is possible that some degree of physiologic hypertrophy occurs, a proliferative phase, with ductal outgrowth and acinar formation, as well as changes in the connective tissue; the onset of menstruation is then followed by regression and desquamation of cells. There is much individual variation in the degree of breast response. Some women experience varying degrees of premenstrual breast discomfort, from a sense of fullness to severe mastodynia. Certainly it is important to know the phase of the menstrual cycle when examining a breast, and if any doubt exists as to physical findings the patient should be re-examined in the midmenstrual phase. It would be helpful to have the date of the last menstrual period recorded on the pathology sheet accompanying a breast biopsy. Not infrequently one receives a report of chronic cystic mastitis in a youthful patient in whom it is difficult to believe that the condition is other than physiologic.

Progesterone is the hormone of the corpus luteum, and thus is actively associated with reproduction. During pregnancy it is also formed in the placenta and at times in the adrenal glands. Progesterone is the least potent of the sex hormones.

Although findings differ in the various experimental animals, breast development apparently occurs as a result of the synergistic actions of estrogen and progesterone. The effect of small doses of estrogen is to stimulate ductal proliferation; large doses result in stunting of the ducts. Prolonged administration of estrogen in experimental animals leads to the formation of cysts similar to those found in hyperplastic cystic disease. Progesterone is responsible for the development of alveoli. After puberty, alveoli and lobules are gradually developed. With the advent of pregnancy there is widespread, irregular growth of alveoli and lobules, with change in connective tissue.

Androgens

Androgens are found in both sexes, and in addition to their function in the development of male characteristics they appear to be essential to the body economy. They promote nitrogen anabolism and influence electrolyte and water metabolism so that the elements necessary for protoplasmic growth are retained—these are sodium, chlorides, potassium and phosphorus.

There is no evidence to suggest that andro-

gens act on the breasts in normal persons. In experimental animals moderate doses do stimulate mammary epithelium, but only when some degree of development has already occurred; they are without effect on epithelium which is not already primed by estrogen. It has been suggested that the gynecomastia which with aspermatogenesis and an increased urinary excretion of FSH forms the Klinefelter syndrome is due to the action of androgens in the absence of a second testicular hormone, inhibin. This syndrome is characterized by normal function of the Leydig cells of the testis. If one accepts the evidence of Warren and Maddock[8] that estrogen is derived from the Leydig cells, then it seems more probable that the condition is a response to estrogen.

The Adrenal Cortex

The adrenal cortex is the source of three main groups of hormones—the mineral or salt-retaining, which originate in the zona glomerulosa; the cortisone group, derived from the zona fasciculata; and the androgenic or nitrogen-retaining hormones, produced by the zona reticularis. This latter area probably is also the source of sex hormone production.

The action of the cortisone group of hormones has been investigated during cortisone therapy and it has been shown that there is an inhibitory effect on the growth of the mammary gland, and that estrogen-induced growth is checked. However, it is possible that during cortisone therapy the steroid metabolism is altered. The administration of ACTH stimulates the production of all adrenocortical hormones, and gynecomastia sometimes follows this therapy.

The adrenal glands apparently are able to take over the function of the ovaries as regards hormone production. Removal of the ovaries in immature animals is followed after an interval by adrenal hyperplasia and tumor formation, with subsequent enlargement of the mammary glands. In women, after the menopause, endometrial biopsy has demonstrated hyperplasia of a type generally associated with hyperfolliculinism. Cyclic vaginal bleeding has been observed in patients following surgical castration. These findings have suggested to Huggins and his co-workers[9, 10] the measure of removing the adrenal glands to eliminate estrogen production entirely in patients previously castrated for breast carcinoma. The same effect of suppressing adrenal function can be obtained by giving cortisone.

The Thyroid Gland

In addition to its role in controlling energy exchange in the body, the thyroid gland is intimately bound with steroid metabolism. One effect of estrogen on the pituitary is to inhibit the production of thyrotropin. The thyroid gland is important in fat metabolism, its action being to decrease fatty acids, cholesterol and phospholipids in the serum. These substances are essential for the synthesis of steroids in the liver.

The presence of either excessive or diminished amounts of thyroid hormone is associated with stimulation of the mammary epithelium. It has been suggested that the thyroid hormone exerts a specific protective influence on breast tissue against harmful steroid effects, and that these effects ensue when thyroid function is altered.

As with the adrenal gland, the presence of a normally functioning thyroid is important to the success of lactation. The administration of thyroid can stimulate waning lactation, but its use must be regulated by signs of thyrotoxicosis.

Role of the Liver in Steroid Metabolism

Zondek[11] was the first to suggest the liver as the site of steroid metabolism, and subsequent experiments have shown that both synthesis and inactivation occur by enzyme action in the liver cells. As is well known, the liver has an enormous safety margin, and gross damage must be present before signs of hormone imbalance appear. The substances cholesterol and choline bulk largely in the processes involved in fat and steroid metabolism. It is probable that cholesterol is the mother substance of the bile acids, and of the sex hormones. A liver component which has received much attention in recent years is folic acid, a member of the vitamin B complex. One

of the main functions of estrogen is the stimulation of tissue proliferation, mainly in the uterus and mammary glands, in adult life. When a deficiency of folic acid was created in experimental animals by the use of the antagonist AMINOPTERIN®, growth was arrested at the stage of rapid cell division. Folic acid appears to be essential to the synthesis of nucleic acid; recently Schoenbach and associates[12] have shown that folic acid antagonists inhibit nucleic acid synthesis in both normal and neoplastic tissues.

Estrogen has been shown to be altered in the liver by enzyme action. When it leaves the liver it is bound to a protein and is inactive. However, it can be converted rapidly to a dialyzable form with the aid of B glucuronidase; this process of "metabolic conjugation" is essential to the utilization of estrogen.

As already mentioned, liver disease must be widespread before signs of endocrine dysfunction become apparent. This may occur in acute infectious hepatitis, or when a previously "compensated cirrhosis" loses ground. In males this is manifested by the appearance of gynecomastia, sometimes accompanied by atrophic cirrhosis, ascites and testicular atrophy, as in the Silvestrini-Corda syndrome. In acute infectious hepatitis high urinary estrogen values are found, with low 17-ketosteroids. Hibbs[13] reported 500 cases of gynecomastia among men who were prisoners of war in Japanese hands; this condition did not appear until about 18 months after imprisonment, and regressed very slowly.

Zondek and Black[14] devised a test of liver function which is significant in both sexes. They found that there was little alteration in the clearance values of endogenous estrogen in the presence of liver damage, but that the excretion of exogenous estrone paralleled liver function and could be a prognostic sign.

Clinical Considerations

One of the fundamental characteristics of breast tissue is its sensitivity to hormone stimulation. The earliest manifestation of this property is the breast enlargement which may occur in either sex during the first two weeks of life. The breasts of these infants show the effect of both estrogen priming and prolactin stimulation, and produce at times a milky secretion known as "witch's milk." This condition may take many weeks to subside.

The breast maintains its infantile contour until it assumes the so-called "bud outline" with the advent of puberty; at this stage the areola becomes elevated and forms with the papilla a small conic protuberance. This stage may be reached before the age of eight years and may be accompanied by other evidence of genital maturation. This precocious puberty is mostly of the constitutional variety, but may rarely be due to a tumor of the hypothalamus, ovary or adrenal. Sometimes mammary development alone may occur in early childhood, indicating an extreme sensitivity to the minute doses of estrogens present during these years.

Usually the breast has assumed the primary mamma shape by about 15 years of age, by which time ovulation has become established. Proliferation occurs both in the epithelial elements and in the stroma, supported by varying amounts of adipose tissue. Localized overgrowth may lead to the development of one or more fibroadenomas, which for some reason are seen more commonly in Negroes. Usually both breasts develop more or less evenly, but occasionally one will become very much larger. Sometimes a diffuse hypertrophy occurs which may be unilateral or bilateral; subtotal mastectomy in these patients proves unsatisfactory because of the disordered state of the physiology.

Normally the male breast does not undergo changes similar to those described above. However, a condition known as simple adolescent gynecomastia occurs at times. This may be unilateral or bilateral and usually subsides in a matter of months. Gynecomastia occurs following estrogen therapy, as in prostatic carcinoma or in the treatment of transvestism; it may also be associated with testicular or liver dysfunction, or with certain tumors such as teratomas or adrenocortical tumors.

When pregnancy occurs, the breasts become hypertrophied and secretion occurs from about the sixth month onward. Lactation usually is established by the third day post partum, and continues while suckling and adequate nutri-

tion are maintained. Involution is usually complete following lactation, but the persistence of groups of ducts and acini in scattered areas may lead to diffuse and painful induration.

Occasionally the presence of milky secretion can be demonstrated for several years following lactation. In rare instances lactation persists and is associated with amenorrhea thought to be of pituitary origin; this is known as the Chiari syndrome.

At the menopause there is gradual alteration in the architecture of the breasts. This was shown by Geschickter[15] to begin in the third decade of life, with irregularity of the lobules and subsequent shrinkage and disappearance of the alveoli. The stroma usually becomes denser due to blending of the various connective tissue components. However, this process, described as senile involution, rarely leads to the complete extinction of mammary tissue. Huseby and Thomas[16] examined a series of apparently normal breasts of older patients before and after estrogen therapy for breast carcinoma and found resultant widespread epithelial proliferation, and in some instances the lobules were indistinguishable from those which occur during pregnancy.

Relation of Physiology to Therapy

Attempts have been made over many years to discover evidences of hormonal dysfunction associated with breast disease. So far there are no consistent findings in urinary estrogens in patients suffering from breast disorders, although most observers think these hyperplastic conditions are due to excess estrogen stimulation. Kier, Hickey, Keettel and Womack[17] devised a method of separating estrogenic and androgenic substances in breast tissue and found in benign breast disease a decrease in androgenic substances, presumably progesterone. Administration of progesterone has been tried without success in these conditions. Androgens have also been given in small doses for severe mastodynia, with equivocal results. Androgens given over lengthy periods will suppress ovulation and menstruation, undesirable effects in these frequently sterile patients. Estrogen compounds may be given over short periods to inhibit secretion, but have no place in the treatment of benign breast disease. Certainly they should be given very cautiously to menopausal patients with a family history of carcinoma.

During the past 15 years there has been increasing interest in the treatment of advanced breast cancer by attempting to alter the endocrine balance of the patient. The use of this type of therapy is restricted to those patients with inoperable primary disease or with recurrent or metastatic disease unsuitable for deep x-ray therapy. As yet there has been little prophylactic use of hormones, though this would be worth considering in a patient with cancer heredity. There are two aspects of influencing the hormonal balance: (1) withdrawal by ablation of certain glands and (2) administration of antagonistic hormones.

One is frequently faced with a decision regarding the suppression of ovarian function, in that many patients with breast cancer experience a late menopause. Interest in this aspect dates back to a Scottish surgeon, Beatson,[18] who in 1896 reported several cases of patients treated by oophorectomy. Castration may be employed as a routine, especially in patients with axillary metastases, *but one cannot overlook the fact that estrogens are frequently produced by the adrenals, especially in young patients.* It is probably better, in the case of a patient in her thirties or early forties, to reserve castration as a therapeutic measure rather than use it prophylactically. Probably it does not make too much difference in the late forties or early fifties. If it is necessary to give androgens to premenopausal patients, then a chemical castration occurs.

Removal of the adrenal glands has been practiced by Huggins in patients who have not responded to castration. The same effect of suppressing adrenal function can be obtained by giving cortisone. Hypophysectomy has also been used when both castration and adrenalectomy have failed. This operation carries a high mortality and is frequently incomplete, leading to diabetes insipidus. This heroic surgery offers little to life expectancy.

Research is still in progress under the Therapeutic Trials Committee of the A.M.A.

as to the optimal dosage of the various hormones. The decision as to which type of hormone to employ is based on the physiologic rather than the chronologic age of the patient. Androgens are given to those who are premenopausal, or 10 years postmenopausal; other patients receive estrogen therapy. Androgens can be given by mouth if necessary, but injection is more satisfactory. Either testosterone propionate or an aqueous preparation of it (androstane or stanolone) can be given in doses of up to 100 mg. three times a week. It is usually several weeks before subjective improvement occurs, such as relief of bone pain and euphoria, with the inevitable virilization. Treatment usually needs to be continued for several months. Estrogens are given by mouth, either as stilbestrol (15 mg. daily), ethinyl estradiol (3 mg.) or TACE® (24 mg.) daily. Treatment may be stopped if the progression is checked, but it is sometimes necessary to switch hormones or to combine therapy. Sometimes digitalis will exert a synergistic action with estrogens. The results of therapy with hormones are variable, but if they are given with care they will do the patient no harm. These are patients with advanced disease, and to make life more comfortable even for a short period seems a worthwhile achievement.

Summary

Breast tissue is extremely sensitive to hormone stimulation, and at various times it is the target organ for almost every hormone produced in the body.

The pituitary hormone, prolactin, is the mammary growth hormone, acting both directly and through the corpus luteum. Estrogen influences growth of the ducts, progesterone that of alveoli and lobules. Prolactin is responsible for secretion, and the posterior pituitary hormone, oxytocin, for milk ejection.

Cyclic breast changes undoubtedly accompany menstruation, with a proliferative phase followed by a secretory phase. Areas of localized overgrowth, with tumor formation, not infrequently are found at the physiologic extremes, the menarche and the menopause.

The efficiency of steroid metabolism can be used as an index of liver function. Liver dysfunction is often accompanied by gynecomastia in males, and can be detected in females by the estrone clearance test. Folic acid, of the vitamin B complex, is essential for the utilization of estrogens, possibly by initiating the synthesis of nucleic acid.

It has been shown that the adrenal gland is capable of supplying the stimulating factors necessary for breast development in the absence of the ovaries. It is important to keep in mind this continuing source of estrogens in a premenopausal patient treated for breast carcinoma.

Although benign breast disease is almost surely due to excess estrogen stimulation, and deficiency of the androgen group of hormones, administration of progesterone or testosterone has been disappointing.

The use of hormones has been quite encouraging in cases of advanced breast carcinoma in which the disease is inoperable or recurrent and unsuitable for surgery or deep x-ray therapy. Androgens are given to premenopausal patients and to those who are less than 10 years postmenopausal, and estrogens are given to older patients. Large and prolonged dosage is essential. Subjective improvement is noted more frequently than objective benefit.

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Diaphragmatic Hernia Caused by Trauma; Diagnosis and Treatment

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TRAUMATIC diaphragmatic hernias result from defect-producing injuries to the diaphragm and constitute an interesting and important surgical entity. Operative procedures to correct this condition are curative in most instances. Without the proper treatment, serious disability or death often results. Today's increased mechanization and speed, combined with recent armed conflicts, have made this a not uncommon condition. Most of the hernias result from gunshot or stab wounds and crushing injuries to the chest. Other hernias, although not due to external violence, follow injury to the diaphragm from the necrotizing effect of an adjacent inflammatory process such as a subphrenic abscess. Recently added are those "arising postoperatively from incisions in the diaphragm."[4]

A characteristic of traumatic diaphragmatic hernias is the absence of a sac of peritoneum. The viscera are therefore free to enter the chest, and all mobile abdominal organs may herniate. The stomach, the small intestine and the colon are the organs most frequently found in the chest. Adhesions between the herniated viscera and the diaphragm or adjacent thoracic structures are usually encountered and increase the hazard of reduction. In addition to the hazard to the abdominal viscera which enter the chest through the diaphragmatic opening, even greater danger to the patient may result from the displacement and compression of the intrathoracic organs.

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As might be expected, most traumatic hernias occur on the left side. The liver is beneath and attached to the right diaphragm; therefore, only the most severe of injuries is likely to produce a hernia on the right. Tears may occur anywhere in the diaphragm, and the crushing injuries produce larger defects than do the penetrating ones. With nonpenetrating injuries, the tear often begins near the esophageal hiatus and extends toward the pe-

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riphery. If the diaphragmatic opening is small, it may be plugged by omentum or covered by liver and may escape detection. Later, a shift in the position of the liver or a sudden increase in intra-abdominal pressure may force the abdominal viscera into the chest, with immediate appearance of the symptoms.

Diagnosis

Diagnosis of a diaphragmatic hernia will not be difficult if one but considers the possibility. The signs and symptoms vary depending on the age of the patient, type of injury, size of the diaphragmatic defect, and identity and condition of the herniated viscera. The history of an old or recent injury such as a penetrating wound of the chest or upper abdomen, or a crushing injury to the chest as in motor vehicle accidents, or a subphrenic abscess, together with symptoms of intestinal obstruction or respiratory distress, should lead one to suspect a diaphragmatic rupture. Young children tolerate pulmonary collapse poorly, so dyspnea is a prominent symptom in them, but in adults the symptoms of intestinal obstruction are likely to predominate.

The diagnosis is made by finding, on physical examination, evidence of compression of the lung and signs of tympany, dullness or audible peristalsis in the lower chest (usually the left). A roentgenogram of the chest in the upright position usually confirms the diagnosis, but difficult cases may require examination of the gastrointestinal tract with barium administered by mouth or by enema. Fluoroscopy is an invaluable aid. Sometimes, pneumoperitoneum, with fluoroscopic examination of the patient in the erect position, is necessary to determine the exact position of the diaphragm. The x-ray findings may include what is thought to be "an abnormally high diaphragm," fluid in the chest, areas of atelectasis, abnormal shadows or gas bubbles, and a shift of the mediastinum to the right. Increasing the intra-abdominal pressure and placing the patient in the Trendelenburg position may aid in demonstrating a suspected hernia.

The following case illustrates a difficult diagnosis which was finally resolved by careful radiographic examination.

Case 1—B. W., a 42 year old white man, was admitted to the Johns Hopkins Hospital on May 30, 1951, complaining of shortness of breath, epigastric pain, and vomiting of two days' duration. The epigastric pain was felt in the left upper quadrant at times and was made worse by coughing. Four years before, this patient had had a series of hospitalizations for treatment of a left subphrenic abscess. This abscess had been drained. Eventually it was found to have arisen from the perforation of a diverticulum of the splenic flexure of the colon. This communication was finally discovered and the colonic opening closed. Incident to these procedures, the spleen was resected.

The patient had been quite well during the interval between the treatment of the subphrenic abscess and the present admission. On admission this time, he was found to have a normal temperature. He appeared somewhat dehydrated. Superiorly and posteriorly over the left chest there was resonance to percussion, but below the fifth rib there was flatness and no breath sounds could be heard. The abdomen was soft, nontender and without spasm. A roentgenogram of the chest showed a collection of gas in the left upper thorax with a large amount of fluid below. The left lung was apparently collapsed. The heart and mediastinal structures were displaced toward the right. Anatomically this was thought to be a hydropneumothorax the origin of which was not clear.

On the day following admission, 800 cc. of cloudy, turbid fluid was removed from the left chest. A culture of the fluid grew coli-aerogenes bacteria. Because of the vomiting, a tube was placed in the stomach and constant suction applied. On the third hospital day, a barium enema showed several irregularities in the splenic flexure of the colon which were attributed to adhesions. The splenic flexure was rather high in the abdomen but the examiner was undecided as to whether it was above or below the diaphragm, especially since the position of the left diaphragm could not be clearly determined.

On the following day, a gastrointestinal series was done following instillation of bari-

um through the stomach tube. The tip of the tube lay in the lower portion of the left thorax. In neither the erect nor the recumbent position did the barium pass higher into the thorax than the tip of the tube. The barium quite readily entered the pyloric antrum and passed into the duodenum. Residual barium remained in the colon, and this organ extended quite far into the left thorax and no diaphragm could be seen above it.

On the fifth hospital day, chest films were repeated, including films made in the lateral decubitus position. Portions of the stomach and the splenic flexure of the colon were high in the left thorax and the diaphragm could not be visualized. At this time, a diagnosis of diaphragmatic hernia was made but it was felt that this diagnosis did not explain the relatively large amount of gas and fluid in the left thorax associated with collapse of the left lung. The possibility of the gas and fluid being in the greatly dilated fundus of the stomach was considered but was thought unlikely. The stomach tube appeared to lie within this viscus, further indicating that the fundus did not contain a sizable amount of fluid. It was suspected, therefore, that some additional abnormality was responsible for the presumed hydropneumothorax. The patient's condition did not improve and surgical therapy was recommended.

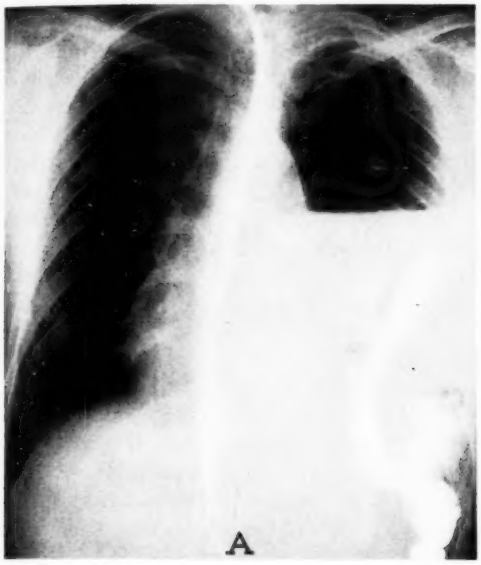
The chest was entered through the bed of the left eighth rib. The operator was amazed to find nearly the entire stomach, the transverse colon and splenic flexure, and several loops of small intestine in the left pleural cavity. These structures were enormously dilated, particularly the stomach, and it was at once apparent that what had been thought to be a hydropneumothorax was, in reality, the enormously dilated stomach which filled the whole upper half of the pleural cavity. The left lung was entirely collapsed. It was possible to reduce the abdominal viscera into the abdomen and to repair the opening in the diaphragm which was circular and about 8 cm. in diameter. The left lung expanded well and the chest was closed.

The patient left the hospital nine days after operation with wounds completely healed and all symptoms relieved. The left lung had reexpanded completely. The patient has been observed regularly, and when last seen on March 22, 1955 there was no evidence of recurrence of the diaphragmatic hernia (figures 1 to 4).

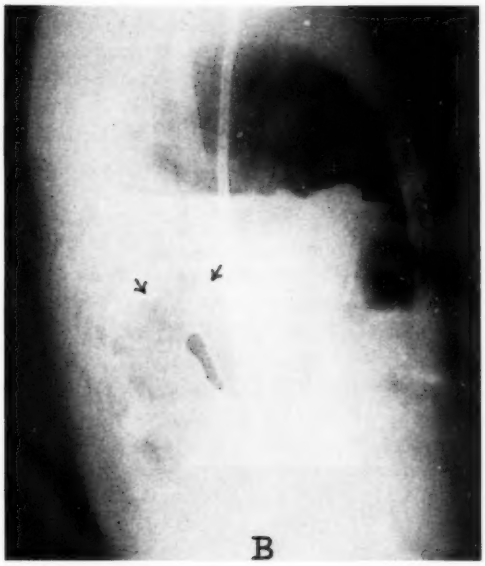
Carter[4] considers the signs and symptoms in three separate phases: those occurring immediately following injury, the interval phase and, finally, the period of obstruction or strangulation. Immediately following injury, the hernia may be overlooked because the symptoms are not specific or the presence of associated injuries may attract more attention. This is particularly true in the blunt, nonpenetrating injuries. Characteristically, the patient complains of left upper quadrant or epigastric pain, which may also involve the lower chest or shoulder. If the stomach is a herniating organ, it may be pinched sufficiently to produce hematemesis; and, with large herniations, pulmonary compression may be sufficient to produce dyspnea and actual cyanosis. Findings on physical examination vary considerably.

FIGURE 1 (case 1). Anteroposterior x-ray of chest taken with patient in erect position. The fluid level with gas above is clearly visible. No lung markings can be seen. The mediastinum is shifted to the right.

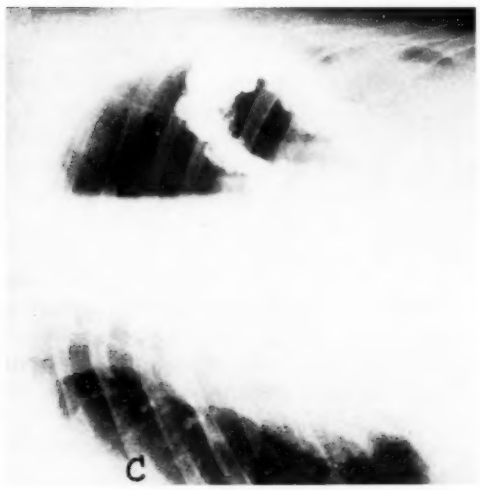
FIGURE 2 (case 1). Three days after admission.

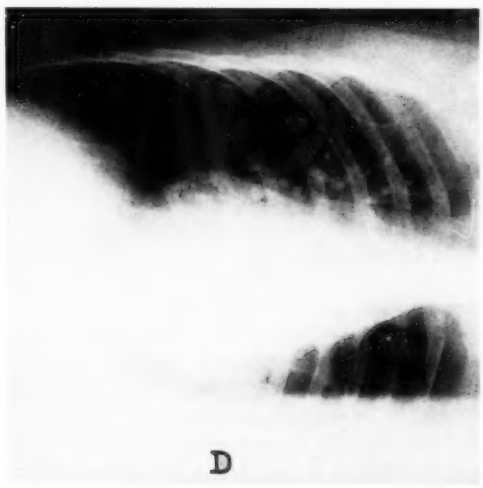


A. A Levin tube has been passed into the stomach. Eight hundred cubic centimeters of fluid had been aspirated from the left thorax (stomach). Some barium remains in the colon and small bowel.



B. Lateral view. The barium-filled intestinal loops can be seen along the fluid level. Arrows indicate suspected position of stomach. At this time the area above was thought to represent a pneumothorax.





C and D. Recumbent lateral views with and without barium which confirm the impression of diaphragmatic hernia.

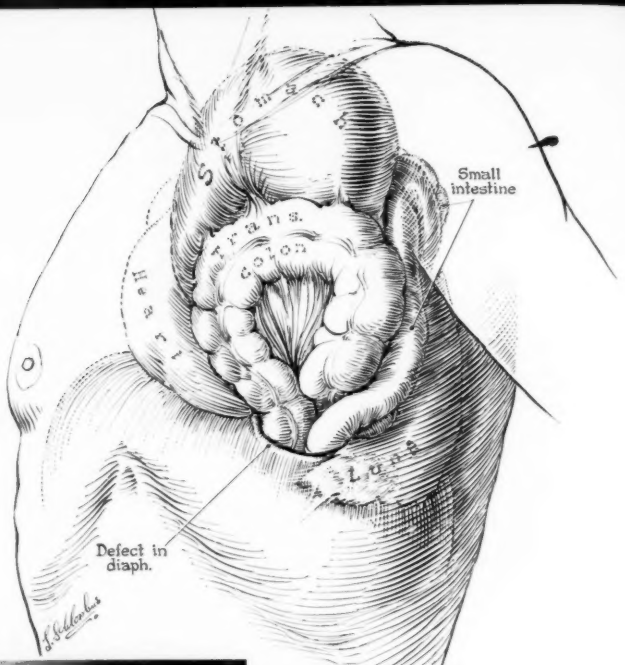


FIGURE 3 (case 1). Drawing illustrating the operative findings, which are quite typical. The stomach is capable of tremendous distention, and it alone can fill most of the chest. Note the size of the diaphragmatic defect and the adherence of the lung to the diaphragm. The mediastinal shift is shown.

FIGURE 4 (case 1). Postoperative x-ray of chest. Some fluid remains at left base, but this subsequently cleared.

and dullness or tympany may be present in the chest, depending on the underlying organ. Mediastinal shift to the right is frequent. X-ray studies may suggest an abnormally high diaphragm but the correct interpretation should not be difficult if they are carefully examined.

If the hernia is not discovered at the time of the accident, it may escape detection indefinitely. The patient may be completely asymptomatic, and only a chance x-ray may demonstrate the presence of viscera in the chest. Vague upper abdominal or lower chest discomfort often associated with meals but not relieved by vomiting, together with respiratory distress on exertion, may suggest the true state of affairs.

The interval between initial injury and the diagnosis of the hernia may vary from a few hours to many years. Often, if the diagnosis is not made at the time of injury it is not dis-

covered until obstruction or strangulation occurs. The incidence of strangulation with traumatic diaphragmatic hernias is high because the defect is smaller than with other types of diaphragmatic hernia. It is estimated that of the cases of strangulation in diaphragmatic hernia, 90 per cent are traumatic in origin. The mortality rate is double once strangulation has occurred. Thus it is essential to establish the diagnosis quickly and to institute proper therapy. Spontaneous recovery is almost unknown.

When strangulation occurs, there is sudden onset of upper abdominal or lower chest pain, and it is not relieved by vomiting. Dyspnea may be pronounced. Physical findings suggest viscera in the chest, and evidence of intestinal obstruction is present in most cases. If the colon is the herniating organ, signs of intestinal obstruction are more prominent than with high obstructions. These signs are absent if the stomach alone is the strangulated organ. "Attention may be focused on the abdomen because of the presence of pain which, as such, is misleading."[4]

The following cases are illustrative.

Case 2—J. B., a 25 year old Negro man, was admitted to Suburban Hospital, Bethesda, Maryland, on October 17, 1951, complaining of crampy abdominal pain associated with nausea and vomiting of about 12 hours' duration. He stated that the pain was in the upper abdomen and para-umbilical area and was intermittent and crampy in nature. He gave a history of having received a stab wound in the lower portion of his left chest about six years prior to admission. Physical examination revealed the abdomen to be somewhat rigid, slightly distended and somewhat tender, particularly in the para-umbilical area. Exploratory laparotomy was performed following the diagnosis of acute appendicitis, and an appendectomy performed. The remainder of the abdominal organs did not attract attention, but the patient failed to improve following return to the ward.

The next day, a thoracic-surgical consultation was requested after x-rays had revealed a high diaphragm on the left with some evidence of pneumonia. Physical examination suggested fluid in the lower left chest, and there was an area of tympany in the midaxillary line. Careful study of the x-rays suggested a diaphragmatic hernia, and with the passage of a Levin tube into the stomach the diagnosis was confirmed. A left thoracotomy was performed and, on opening the pleura, considerable bloody, foul-smelling fluid was encountered. The left lower lobe was partially collapsed, and a fist-sized mass presented through the apex of the diaphragm. It was covered with omentum and found to be necrotic, perforated, transverse colon. Approximately 10 in. of this colon had herniated through a 1 in. opening in the dome of the left diaphragm, and all of the bowel in the chest was necrotic. There was a perforation in the ascending loop which had allowed gross contamination of the entire left chest. The ring of the defect obviously had constricted the blood supply to the bowel.

The diaphragmatic defect was enlarged sufficiently to allow resection of the gangrenous colon, and an abdominal double-barreled colostomy. Following this, the defect was closed and the pleural cavity drained and closed in layers. The postoperative course was stormy and prolonged. An empyema developed in spite of the water-seal drainage. This required rib resection and, finally, pulmonary decortication. The continuity of the bowel was reestablished, and the patient slowly recovered. He has been well since that time (figures 5 and 6).

Case 3—C. W., a 25 year old white woman, was in an automobile accident in which she received a severe nonpenetrating crushing injury to her chest and upper abdomen. Internal injury was not suspected at the time. Soon thereafter, she began to complain of vague pain in the upper abdomen and lower left chest. At times there was vomiting, and she had occasional dyspnea on exertion. Because of the persistence of these symptoms, eight months following injury x-ray studies were performed. An erect plain roentgenogram of the chest suggested the presence of abdominal viscera above the left diaphragm. This was dramatically confirmed by a barium enema, which revealed the major portion of the trans-

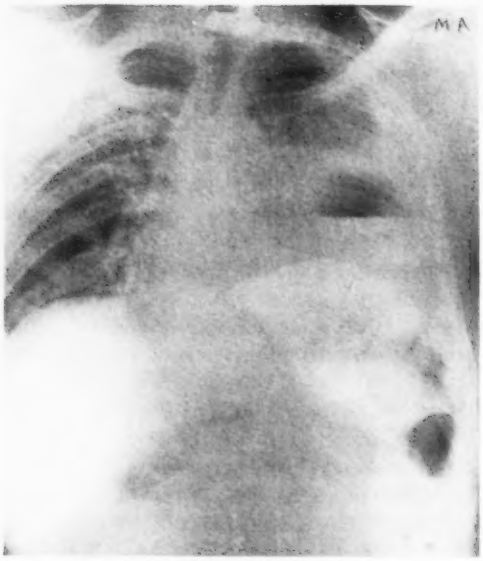


FIGURE 5 (case 2). Anteroposterior x-ray of chest taken with patient in erect position. Note how the gas and fluid level in the herniated colon suggests the gastric bubble. The left diaphragm appears high, but the true position of the diaphragm cannot be identified. The atelectasis and mediastinal shift are marked.

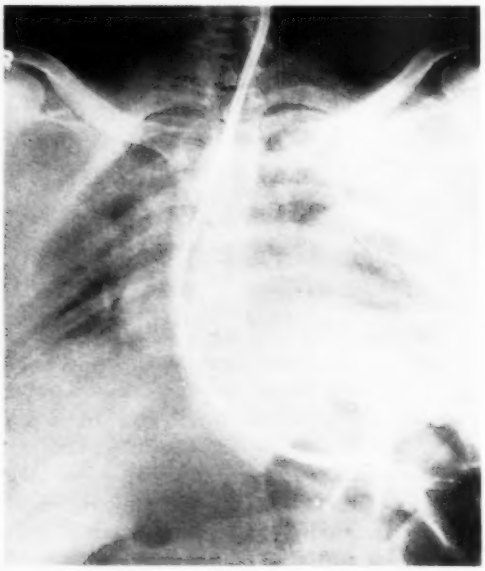


FIGURE 6 (case 2). A Levin tube has been passed into the stomach and shows it to be well below the suspected region of the diaphragm. The rim of collapsed lung around gas-filled bowel has the dome-shaped appearance of the diaphragm.

verse colon extending almost to the apex of the left chest. The diagnosis of traumatic diaphragmatic hernia was made and surgical correction strongly recommended. The patient, however, refused operation. Her symptoms persisted, and about one year following the injury she became pregnant. The symptoms increased in severity as pregnancy progressed and, finally, during labor, approximately 20 months following her initial injury, she died of severe respiratory distress and intestinal obstruction.

This tragedy might have been prevented had the patient submitted to operation. This case demonstrates how the diagnosis may be overlooked at the time of injury. The patient tolerated the hernia well even though symptoms were sufficient to lead to the correct diagnosis before strangulation had occurred. The role of pregnancy in this case is important since, with the enlarged uterus, the intra-abdominal capacity was markedly decreased. The increased intra-abdominal pressure associated with straining during labor probably forced most of her mobile viscera into the left chest (figures 7 and 8).

The differential diagnosis includes eventration of the diaphragm, pneumonia, atelectasis, intrathoracic cyst or tumor, pleural effusion or empyema, and pneumothorax. The condition may be thought to be primarily a pulmonary one, such as an empyema, and the underlying cause only discovered later. Pulmonary embolism, coronary occlusion, and pain from gallbladder disease or peptic ulcer have been suggested as possible diagnoses in some cases.

The following case report illustrates the difficulty.

Case 4—A young white soldier sustained a penetrating shell-fragment wound of the left chest during the Battle of the Bulge (December 1944). The wound of entrance was in the left anterior axillary line in the sixth interspace, and there was no wound of exit. The resulting left hemothorax was treated by aspiration, with good expansion of the lung. He was evacuated to the United States within two weeks of injury. He appeared to be convalescing uneventfully and was afebrile and up

walking about. Roentgenograms showed a small metallic fragment near the spine in the soft tissues of the posterior left thorax.

About six weeks after injury, while resting in bed, he suddenly complained of pain in the left chest and became dyspneic and cyanotic, and his blood pressure fell to shock levels. He was thought to have had massive pulmonary embolism. The respiratory distress continued and he died two hours after onset of symptoms. Autopsy revealed a small opening in the left diaphragm through which the stomach, transverse colon and several loops of small intestine had herniated. The left lung was completely compressed and the mediastinum was displaced to the right.

Treatment

The treatment for traumatic diaphragmatic hernias is surgical. Unless obstruction has occurred, sufficient time can be allowed to prepare the patient adequately for operation. Intestinal intubation with decompression of the stomach and upper bowel may be lifesaving. The danger of strangulation is the most urgent indication for operation. Once strangulation has occurred, time is of the essence and the procedure is considered an emergency. The thoracic approach is preferable to the abdominal one because of the superior exposure which avoids the hazard of blind reduction of viscera which may be adherent to the diaphragm, lung or chest wall. The herniated viscera are replaced into the abdomen, the diaphragmatic defect is repaired, and the collapsed lung re-expanded. Following operation, healing is aided by avoidance of tension on the suture line, and it is important to combat abdominal distention and to prevent any undue exertion.

The following brief case reports illustrate some of the important aspects of various problems in the diagnosis or treatment. Cases 5 and 6 presented problems in the management and repair of acute severe injuries to the diaphragm, while cases 7 and 8 illustrate problems due to late repair of old injuries.

Case 5—E. B., a 34 year old Negro man, was admitted to Suburban Hospital, Bethesda, Maryland, on November 15, 1952, for treat-

FIGURE 7 (case 3). Plain anteroposterior x-ray of chest taken with the patient erect. Viscera are clearly visible in lower left portion of chest.

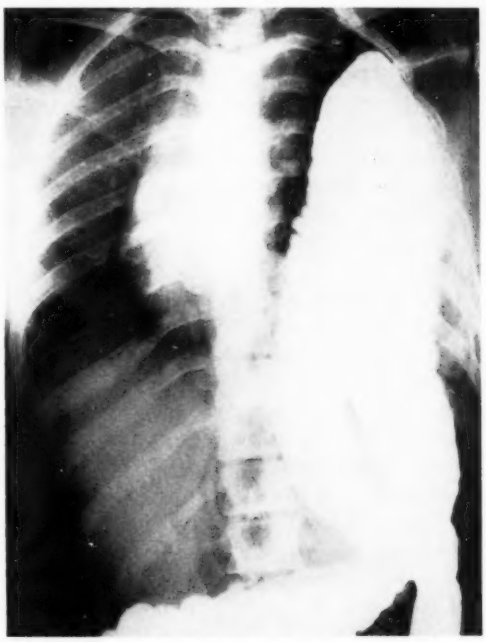


FIGURE 8 (case 3). Barium enema demonstrating transverse colon extending almost to apex of left chest. Note the narrow area in the diaphragm through which the ascending and descending limbs of the colon pass.

ment of a gunshot wound of the right chest. He stated that a 20-gauge shotgun, with which he was playing, had dropped to the floor and discharged. The blast at close range struck his right chest in the midaxillary line at the level of the tenth rib. Had the patient not been a 260 lb. man with a very thick chest wall, the likelihood that he could have survived the initial injury is rather remote. He was conscious, but in shock, on arrival in the accident room, and a fist-sized defect in the lower chest was bleeding vigorously. The entire thickness of the chest wall, together with a portion of the right lobe of the liver and much of the right diaphragm, was completely avulsed or macerated, and part of the remaining liver had herniated through the diaphragmatic defect into the right chest. Pieces of clothing, shell wadding, shot and necrotic muscle were found scattered throughout the lower chest.

Immediate operation was undertaken. The damaged tissues were débrided, the foreign material was removed, the liver bleeding was controlled with ligatures and GELFOAM® packs, the liver was replaced into the abdomen, and the diaphragmatic defect was repaired. A catheter was brought out of the chest and attached to water-seal drainage. An empyema did not develop. Intestinal decompression was accomplished by intubation and withholding oral fluids. He was given only parenteral fluids for 48 hours. His recovery was uneventful.

Comment—This case represents a penetrating injury to the diaphragm which was repaired immediately. Had the injury occurred on the left, much of the viscera undoubtedly would have herniated, but because of the position and size of this defect, only liver could enter the chest. Had this defect been produced by a nonpenetrating injury, operation probably could have been delayed. Primary healing is to be expected if careful repair of the defect is aided by attempts to prevent undue pressure on the suture line as with abdominal distention (figure 9).

Case 6—H. W., a 40 year old white woman, was admitted to the Johns Hopkins Hospital on August 24, 1951, for treatment of a self-inflicted shotgun wound of the lower left chest and upper abdomen. Her history revealed that she had been suffering from severe depression for many years and had made repeated suicidal attempts. The present one consisted of placing a 20-gauge shotgun against her upper abdomen and firing it. A large defect in the anterior portion of the left diaphragm was produced, and it was torn from its chest wall attachments over the anterior portion. There were puncture wounds of the left kidney and adrenal gland. Immediate operation consisted of a thoracico-abdominal exploration of the wound with débridement of the damaged tissues, resection of the splenic flexure of the colon with an end-to-end anastomosis, splenectomy, and repair of the diaphragm. The latter consisted of attaching the remaining portion of the diaphragm to the remnants of the intercostal muscles and the posterior aspect of the rectus sheath. Large quantities of blood and antibiotics were given, and the patient's blood chemistries maintained in a satisfactory state by electrolyte administration. Her postoperative course was stormy and complicated by a moderate empyema, which was drained, and by the necessity for re-exploration to remove buckshot from portions of the lateral chest wall. Finally, the infection cleared, the diaphragm appeared to heal normally and maintain some motion, and

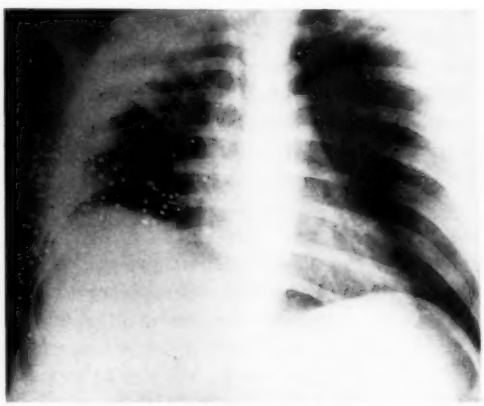


FIGURE 9 (case 5). Anteroposterior x-ray of chest reveals some of the shot scattered throughout lower chest. The herniated liver can be seen in the lower right chest. The pneumothorax, atelectasis and evidence of fluid are demonstrated.

she was discharged to a psychiatric institution for further therapy.

Comment—One of the most interesting aspects of this case is how the patient was able to survive the initial injury. Fortunately, little of the diaphragm was actually lost, and the injury stripped the attachments rather than avulsed tissue. Damage to the colon was ideally treated by resection and primary anastomosis in contrast to the necessitated colostomy in case 2.

Case 7—A. S. was admitted to the Johns Hopkins Hospital on January 8, 1954, for treatment of a traumatic diaphragmatic hernia. The patient stated that he had received a shrapnel wound in his left lower back during the Spanish Revolution in 1936. Soon thereafter an empyema developed which required three operations for drainage, at least one consisting of rib resection. The involved left lung was collapsed but finally re-expanded after about seven months. Immediately following injury, the patient experienced shortness of breath on exertion, associated with a sensation of "gas gurgling in the left chest." He noticed fullness in the left chest after eating and was unable to sleep lying on his right side. There was no vomiting or pain in the chest. The feeling of tightness or pressure was intensified if he went to bed soon after the evening meal. X-rays finally were taken which revealed a diaphragmatic hernia. Physical examination revealed a healthy-appearing young male who did not complain of any discomfort, but eructated frequently. There was a well-healed, 12 cm. scar on the posterior aspect of the left chest. The right lung was clear to percussion and auscultation, but on the right side the breath sounds were markedly diminished, and bowel sounds were readily audible in the axillary region. Repeat x-rays including gastrointestinal series confirmed the admitting diagnosis. On January 15, 1954, the patient was subjected to transthoracic repair of the diaphragmatic hernia, from which he made an uneventful recovery.

Comment—The initial injury must have produced the diaphragmatic defect. Dyspnea and "gurgling in the chest" should have made the diagnosis easy. The difficulty in lying on his right side can be explained by the pressure of the herniated viscera on the mediastinum shifting it against the opposite lung. All such patients feel a sense of pressure from the pulmonary constriction and mediastinal compression. The pain following meals is identical to that seen with hiatal hernias in which the stomach fills with food or air as it lies above the diaphragm, and with this distention there is a feeling of pressure and constriction in the region of the defect. Often, standing and walking about will aid reduction of the herniated viscera.

Case 8—J. L., a 60 year old white man, was admitted to the Johns Hopkins Hospital on December 17, 1954, for repair of a traumatic diaphragmatic hernia. He had been injured in a mining accident 24 years prior to admission, at which time he suffered a fractured pelvis and multiple lacerations. He was crushed, but there were no penetrating injuries. The fracture necessitated hospitalization for almost three months. Soon after injury, it was noted that he experienced nausea after meals and there was left upper quadrant discomfort and exertional dyspnea, particularly after large meals. X-ray examination revealed a diaphragmatic hernia, but the patient was advised that "nothing could be done." The dyspnea and nausea continued, and he began to experience considerable discomfort following meals or after lying down. He said that often he could feel the viscera slip from his chest, with relief of the dyspnea. Physical examination revealed dullness over the posterior left chest with bowel sounds clearly audible over most of the left chest. X-rays demonstrated the presence of the stomach, small bowel and splenic flexure of the colon lying above the diaphragm in the left chest.

On December 18, 1954, through a transthoracic approach, the viscera were found in the left chest, compressing the lung and displacing the mediastinum to the right. There was a 10 cm. defect in the left leaf of the diaphragm where it had been stripped from its attachments to the rib cage. A hernial sac was not present, and there were no adhesions between the herniated viscera and the thoracic organs. Attempted reduction of the abdominal

viscera was difficult, and this finally was accomplished by making a left paramedian abdominal incision to aid in the reduction. The diaphragmatic defect was repaired utilizing tantalum mesh, following which the abdominal and chest wounds were closed.

The postoperative course was complicated by abdominal distention and persistent pneumothorax in spite of a catheter, and it was assumed that the lung had been torn during re-expansion. Inadvertent dislodgment of the chest catheter necessitated its later reintroduction because of the tension pneumothorax. Intestinal intubation and PROSTIGMIN®, PITRESSIN® and other intestinal stimulants were necessary to combat the paralytic ileus. Complete recovery followed.

Comment—In this instance it was possible to make the diagnosis early because of the complaints of dyspnea, nausea and epigastric pain. Typical was the complaint that the pain was worse following meals and that dyspnea accompanied this and lying down. The explanation for this obviously is that, with distention of the stomach following meals or in the prone position, more viscera occupy the thoracic position. Patients often resort to standing or jumping to reduce such hernias. The failure to find adhesions and the fact that the diaphragm was torn from its attachments rather than split are uncommon. Abdominal relaxation in order to accomplish reduction of the hernia is a useful aid but not often necessary. The utilization of tantalum to strengthen the repair probably works better than cutis grafts or fascia, but in this case it is conceivable that a rough edge on the tantalum mesh was responsible for the continuing tension pneumothorax.

Summary

The occurrence of symptoms of intestinal obstruction and or those of pulmonary compression in a patient with a recent or old wound of or injury to the chest or upper abdomen or a history of subphrenic abscess should lead to a suspicion of diaphragmatic hernia. The diagnosis usually can be made by careful physical examination and can be confirmed by roentgenographic studies. Operative repair is the treatment for traumatic diaphragmatic hernia. Several case histories illustrate problems in diagnosis and therapy.

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Intestinal Obstruction in the Newborn

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DURING the hours of earliest life, the onset of intestinal obstruction is heralded by a group of signs and symptoms which make it possible for the observant clinician to diagnose the condition with accuracy and to afford appropriate surgical care with celerity. Since the newborn child tolerates surgery notably well but resists the ravages of dehydration and peritonitis poorly, the great advantages to be derived from prompt diagnosis are of paramount importance. A profitable approach may therefore be constructed about these groups of signs and symptoms.

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Expectoration or Vomiting, Without Prominent Distention, During the First 72 Hours of Life

Clinical observations and diagnostic procedures—1. Careful note must be taken of any respiratory or circulatory difficulty associated with the vomiting—cyanosis, retraction or peripheral collapse. Congenital hernia through the diaphragm may affect the digestive, circulatory or respiratory system and may show a first sign referable to any of these systems.

2. Observation of presence or absence of bile in the vomitus. The presence of bile affords unequivocal evidence that the obstruction, if present, is either incomplete or beyond the second portion of the duodenum.

3. A gastric tube should be passed. Its position may indicate a diaphragmatic hernia or an esophageal atresia. It is a useful tool for ridding the stomach of inspissated mucus or

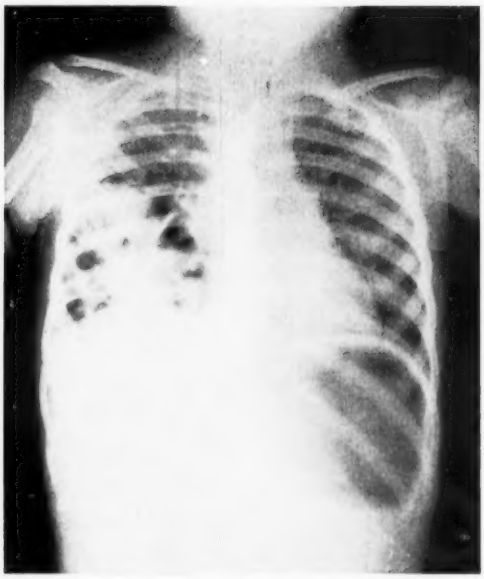

FIGURE 1. Congenital hernia through the right side of the diaphragm is indicated by the abnormal gas shadows in the right thorax. This hernia presented through the right pleuroperitoneal gutter (foramen of Bochdalek).

FIGURE 2. Esophageal atresia with tracheo-esophageal fistula into the distal esophageal segment. Radiopaque medium outlines the proximal blind pouch of esophagus, while the presence of air throughout the intestinal tract demonstrates the fistula.

for introducing a radiopaque material prior to x-ray examination.

4. X-ray examination of the chest and abdomen should be carried out. Attention must be directed toward the presence of abnormal gas shadows in the thorax, toward the position of the tube, if present, and toward the pattern of the intraluminal gas.

Synthesis—The absence of distention marks this group. Here are found the congenital diaphragmatic herniations, the esophageal atresias, and the duodenal atresias or diaphragms. These serious anomalies far overshadow in number and significance the rare chalasia, cardiospasm, gastric lesion or annular pancreas which may cause vomiting without distention.

1. The diaphragmatic hernia is diagnosed by any sign, visible or audible, indicating that abdominal viscera are displaced into the thorax (figure 1). Vomitus will contain bile, as a general rule. Radiopaque media usually are not needed to confirm the diagnosis. The extreme rapidity with which circulatory collapse may ensue upon the earliest onset of symptoms has made us regard this as a most urgent emergency in the neonatal period.

2. Esophageal atresia occurs most commonly in conjunction with a tracheal fistula communicating with the postatretic esophageal segment. X-ray reveals a tube or radiopaque medium to be retained within the blind, dilated proximal esophageal pouch, which usually ends at about the level of the third rib posteriorly. The stomach and intestine are characteristically filled throughout with gas which has entered through the fistula (figure 2). The proximal cul-de-sac is, of course, constantly filled with secretions which are the source of the excessive expectoration. This affords the earliest clue to the presence of the anomaly. Bile does not appear. The very overflow of secretions which causes the expectoration is also the cause of the aspiration which leads to the rapid onset of pulmonary complications. Surgery must be offered forthwith to abort the aspiration and the inevitably fatal

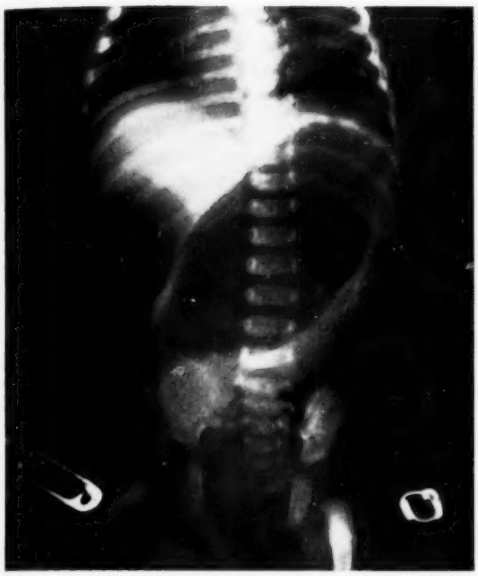

FIGURE 3. Duodenal atresia is demonstrated by the massive dilatation of the stomach and duodenum. The absence of air in the lower intestine indicates complete obstruction. The lesion involved the second portion of the duodenum.

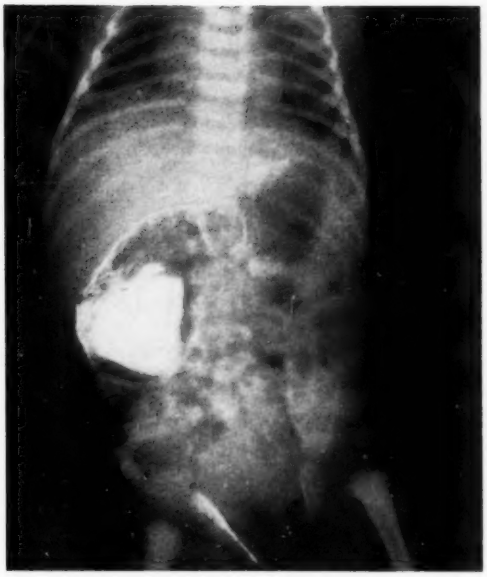

FIGURE 4. Duodenal stenosis is demonstrated by the massively distended stomach and duodenum. The pyloric ring can be seen. The obstruction is at the level of the ligament of Treitz. The passage of barium and air into the jejunum indicates a partial obstruction (stenosis).

pneumonia. Time, however, should be taken to correct blood, electrolyte or water deficits and to begin antibiotic therapy.

3. The duodenal atresia or diaphragm is a diagnosis to be made by x-ray. While bile is commonly present in the vomitus (most duodenal obstruction occurs low), an occasional diaphragm involves the duodenum proximal to the ampulla of Vater. The x-ray shows the gaseous distention of the stomach and the duodenum without evidence of gas beyond (figure 3).

Duodenal stenosis may be rather more difficult to diagnose because of its more insidious onset and because of the presence of gas shadows in the bowel beyond the duodenum. The distention of the duodenum proximal to the point of stenosis affords the diagnostic clue. The stenosis occurs most characteristically at the level of the ligament of Treitz (figure 4).

Treatment—1. We have emphasized that the congenital diaphragmatic hernia cannot be regarded too gravely. It is preferred that operation be deferred only long enough to pass an intestinal tube and to assure an intravenous entrance by plastic or metal cannula.[1] The formation of the diaphragm from its several embryologic components tends to leave weak areas posterolaterally and retrosternally. The great majority of these hernias occur through the left pleuroperitoneal foramen (left foramen of Bochdalek). All these hernias are readily repaired through a transabdominal approach. Occasionally it has proved necessary to introduce a finger through an intercostal space to replace a solid viscus, or to permit air to enter the pleural space through the hernia ring to facilitate replacement of hollow viscera. After the organs have been replaced, examination of the diaphragmatic defect reveals a rim of tissue which can be sutured. We have utilized interrupted mattress sutures for this purpose.

The control of postoperative distention and the accurate maintenance of fluid and electrolyte balance are mandatory if success is to at-

tend the surgeon's efforts. The time which is necessary for the bowel to return to normal function depends, among other factors, on the trauma during the period of incarceration and subsequent replacement, and on its degree of distention at the time of operation. During the period of postoperative ileus, the survival of the patient is directly and almost solely dependent on the skill of the pediatric management.

2. Atresia of the esophagus, as already mentioned, is commonly associated with tracheo-esophageal fistula. In those cases, fortunately a minority, where the fistula is associated with the proximal segment, the continuous flow of pharyngeal secretions into the tracheobronchial tree leads to a rapid pneumonia and a dire prognosis. In the more common anomaly, with a distal fistula, figures for cure range from 25 to 50 per cent.

We attempt, whenever possible, to carry out a primary anastomosis between the ends of the esophagus. The mediastinum is approached from the right side. The generous exposure afforded by the transpleural approach has attracted many proponents.[2] We have preferred to utilize an extrapleural approach, feeling that the incidence of pulmonary complications is lower. Originally, short segments of the third, fourth and fifth ribs were excised paravertebrally. We now resect a full length of the right third or fourth rib and strip back the pleura. We feel that the exposure through this approach has been ample. Whenever adequate lengths of esophagus can be mustered, anastomosis by silk suture is carried out. Wide mobilization of the hypertrophied proximal segment is carried high into the neck.

If anastomosis has proved impossible, cervical esophagostomy and gastrostomy have been carried out, deferring re-establishment of continuity to a later date.

Some degree of stricture (usually slight) at the suture line occurs in almost half of these patients. This yields readily to bougienage or retrograde dilatation with the Tucker dilators.

3. Duodenal obstruction due to atresia or diaphragm is amenable to surgical correction by bypass of the obstructed segment. Immediate operation may be undertaken in cases where vomiting has not been protracted and dehydration and electrolyte imbalance have not become prominent features of the illness. If these complications have supervened, adequate time may be taken to correct the deficits. In either event, nasogastric suction should be utilized to decompress the dilated stomach and duodenum, the suction being maintained throughout and following the operation.

Operation is preferably directed toward the completion of a duodenojejunostomy about the obstruction. Occasionally, the duodenal anomaly is so high as to necessitate a gastrojejunostomy. The theoretical danger of marginal ulcer and the more normal anatomy of the duodenal anastomosis incline one toward the latter. Suture is carried out with one layer of continuous inverting silk, reinforced as needed with interrupted Halsted mattress sutures.

Where a diaphragm, rather than an atresia, seems to be the culpable lesion, excision of the diaphragm with a Heineke-Mikulicz closure of the duodenum may relieve the obstruction. Since simple division of such a diaphragm is too often followed by recurrence of the obstruction, one is well advised to err on the side of anastomosis in preference to local attack on the lesion.

A percentage of cure somewhat better than 50 per cent accompanies surgical attack on these lesions. Morbidity can be reduced by exercising caution in the resumption of feedings. It has been our custom to withhold oral feeding and to maintain suction for 48 hours following operation. Five cubic centimeters of 5 per cent glucose is then offered hourly and, if tolerated, feedings are rapidly increased.

Similar considerations govern the treatment of duodenal stenoses. In our experience it has been necessary to proceed somewhat more cautiously in resuming feedings following correction of these, allowing, occasionally, five to seven days before even small amounts of glucose solution proved acceptable orally.

Vomiting and Distention in the First 72 Hours of Life

Clinical observations and diagnostic procedures—1. Careful note must be made of the

appearance of meconium. Sherry and Kramer[3] have established that 99 per cent of all full-term children have passed meconium within the first 48 hours of life. Failure of a child to do this must be regarded as an ominous sign.

2. Note must be taken of palpable masses (of feces or meconium) in the abdomen.

3. X-ray of the abdomen to permit study of the gaseous shadows and the presence of abnormal intra-abdominal shadows.

Synthesis—The presence of distention in this group permits the reasonable conclusion that the obstruction is one which is occurring lower in the intestinal tract than the conditions discussed in the first group, or that the lesion involves diffusely a great portion of the whole alimentary tract. Three important abnormalities most commonly account for this syndrome: (1) atresia, and stenoses of the lower bowel (usually the ileum), (2) meconium ileus or peritonitis and (3) malrotations of various types.

1. The considerations governing atresia and stenoses of the lower intestinal tract are grossly similar to those discussed under the duodenum. The ileum and duodenum are the most common sites for this anomaly, which theoretically represents a failure of reluminization of the fetal bowel. While the infant may pass a meconium stool from the accumulation of fetal detritus, normal passages will not occur thereafter. Indeed, examination of the meconium for squamous cells, after the method described by Farber, fails to reveal them, demonstrating an absence of continuity between mouth and anus. X-ray examination of the abdomen reveals dilated loops of bowel to the point of obstruction. It is obvious that the lower the obstruction the greater will be the distention and the greater the number of loops visualized on x-ray. The gaseous shadows, in contrast to what will be mentioned below concerning the "meconium" disorders, are uniform and large (figure 5). If barium enema examination is performed (although this is unnecessary), the colon will be seen to be small in caliber.

2. Meconium ileus is a manifestation of what is now generally understood to be a systemic disease characterized by Schwachman and associates[4] as "mucoviscidosis." In this illness, the salient feature of which is an increased viscidity of all bodily secretions, the intestine becomes obstructed by an incredibly tenacious meconium which is of this consistency because of the failure of pancreatic secretions to act upon it. The latter is due not to pancreatic deficiency per se but apparently to an inability of the secretions to reach the intestinal tract. (This latter phenomenon, too, accounts for the viscid pulmonary secretions which preclude adequate bronchial drainage and cause the chronic pulmonary infection.)

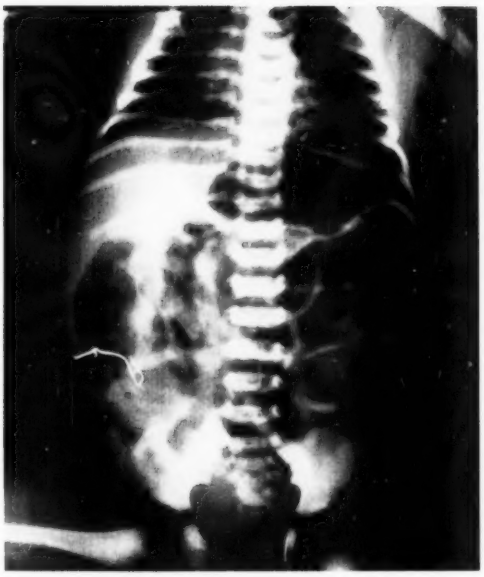

FIGURE 5. Low ileal obstruction is indicated by the multiple dilated loops of bowel filling the abdomen. The gaseous distention tends to dilate the intestinal loops uniformly.

Children die of this disease in two phases: in the neonatal period, of intestinal obstruction; immediately, and at any time thereafter, of pulmonary infection and sepsis. The pancreatic deficiency in itself does not appear to be a serious handicap.

The disease can be diagnosed on two findings: (1) the failure to pass meconium and (2) a rather characteristic x-ray picture. Abdominal x-ray reveals a blotchy gas pattern,

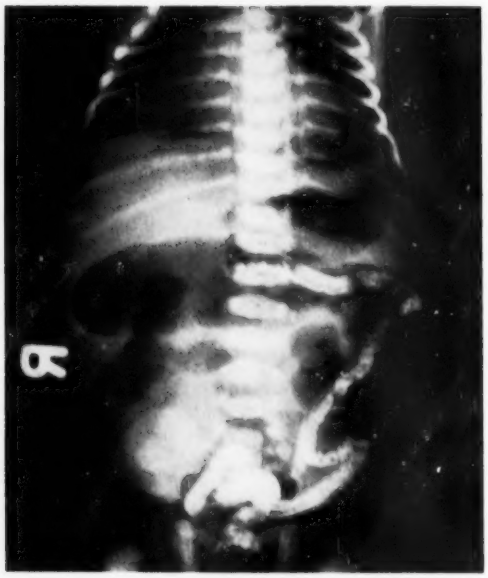

FIGURE 6. Meconium ileus with obstruction is indicated by the distended loops of bowel, granular shadows of meconium, and lack of uniformity of size in the gas-filled loops. The barium enema, while contributing nothing to the diagnosis, illustrates nicely the small caliber of the colon, which has as yet experienced no passage.

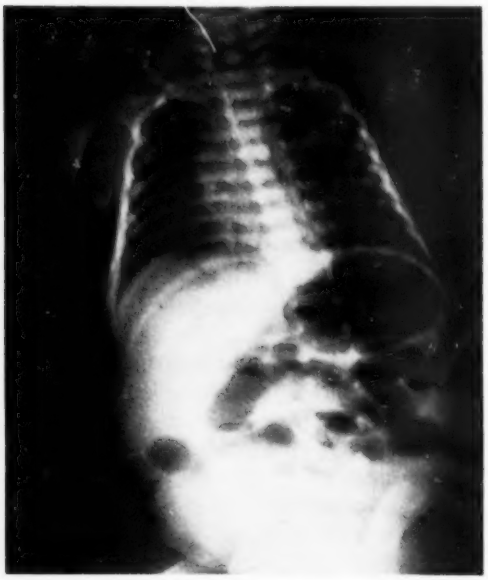

FIGURE 7. Meconium peritonitis, old or new, is indicated by the calcific shadows in the right lower quadrant, where bits of meconium in the peritoneum have calcified.

the collections varying in size (in contrast to the atresia), and often shows areas of collected meconium, represented as mottled segments in the bowel (figure 6).

The presence of calcific shadows implies that meconium has been in the free peritoneal cavity and has become calcified, the so-called meconium peritonitis (figure 7). This latter disease may occur as part of an existent mucoviscidosis, in which case the newborn infant will fail to pass meconium and will be governed by the same considerations as other cases of meconium ileus. Meconium peritonitis also may be seen with obstruction when the child passes meconium normally. In such a case it is assumed that adhesions from the prenatal peritonitis are causing the obstruction, rather than inspissation of meconium.

3. Malrotations involve a number of abnormalities ensuant on failure of the intestine (primarily colon) to complete its normal involved and complex movement from left to right in the abdomen. Normally the cecum assumes its position in the right lower quadrant, and the duodenum, ascending colon and descending colon are established as retroperitoneal organs as a result of these rotations. Failure of rotation not only results in the bowel's assuming an abnormal anatomic situation, not serious in itself, but also causes peritoneal reflections to extend across the abdomen in unusual configuration. These reflections or bands may cause obstruction as they traverse loops of bowel. In addition, and extremely important in that it is a very frequent accompaniment of malrotation, the small bowel mesentery is shortened and inadequately fixed posteriorly, permitting volvulus of the whole small bowel. The latter, which infrequently causes closed-loop obstruction with a concurrent strangulating process, is extremely grave. In the presence of obstruction from bands, the characteristic x-ray picture is not dissimilar to that in an atresia. In volvulus, however, the air entering the twisted loop occasionally will demonstrate a characteristic spiraling (figure 8). Shock supervenes rapidly in the latter condition, because of intraluminal bleeding. As with the atresia, meconium is usually passed, but stool fails to appear.

Treatment—1. While it is obvious that what has been said concerning atresias and stenoses of the duodenum must obtain for atresias of the lower bowel, two or three points bear emphasis. The infant with lower intestinal obstruction will be more characteristically dehydrated. This is due to the somewhat longer period during which the disease has existed prior to the onset of vomiting, and to the actual fluid loss into the dilated loops of bowel. It behooves one, therefore, to provide adequate restoration of fluids before embarking on the operative procedure.

The operation itself consists of establishing an anastomosis between the interrupted segments of bowel. In contrast to the duodenum, where mobilization is usually precluded, direct repair of the jejunum or ileum is accomplished with ease. The anastomosis is carried out end-to-end or end-to-side, as circumstances and the size of the bowel loops may dictate. The colon, never distended by the passage of stool, is extremely small in caliber, but is not, in contrast to opinions previously held, hypoplastic. It dilates immediately on passage of stool, offering no apparent impediment to its passage. The saline enemas advocated by some authors for dilatation of the colon have not proved to be necessary.

Postoperatively, we have withheld feeding from these children, maintaining suction by tube in the stomach or intestine. When the passage of stool or gas has indicated a normally functioning tract, we have begun the feedings.

2. Meconium ileus is attacked by the surgeon to relieve the child of his intestinal obstruction. In order to appreciate the problem, one must ponder the obstructing mechanism. Ordinarily, on entering the abdomen, the surgeon is confronted by a small bowel progressively greater in distention to a point somewhat proximal to the ileocecal valve. Here a loop of ileum is engorged with an incredibly tenacious meconium which clings to mucosa and rubber glove alike. As one proceeds proximally from this, there is usually much less meconium, and the meconium itself is somewhat less mucilaginous. The distal ileum usually contains a few inspissated bits of fecal

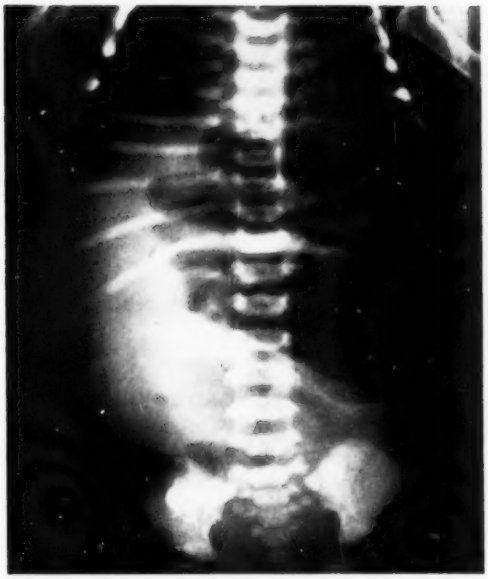

FIGURE 8. A volvulus of the midgut is indicated by the air-filled, spiraling loops of bowel in the left upper abdomen. The relative opacity of the rest of the abdomen is due to the obstruction which has prevented passage of gas or fluid into the colon.

matter which can be moved into the colon if the operator wishes. They are of no apparent significance. The colon is normal, but has a small caliber. The problem is to rid the bowel of its meconium.

It is known that pancreatin solutions will dissolve the abnormal meconium. It has been claimed by some that vigorous saline flushing will help to remove it. The mechanical difficulties accompanying such methods are well known to any surgeon who has tried them. We have found it most expeditious to proceed as follows: We have disregarded all bowel distal to the area of meconium collection. If the principally involved loop has been of reasonable length, we have resected it, and, with its stoma outside the abdomen, have irrigated the bowel proximal with pancreatin solution until it was clear. We have then placed a single continuous row of silk suture between the posterior wall of the proximal and distal ileum, creating, in effect, a loop ileostomy. The ab-

dominal wall has been closed around this. This has permitted an appreciable overflow of secretions into the distal loop, to the benefit of the bodily economy. We have not designed a spur, feeling rather that the loop method held the advantages of speed and of fluid conservation.

Where the loop of bowel containing the bulk of the meconium has been very long, we have removed only a portion, and have irrigated out the remainder. In the event that multiple segments were involved, we have utilized multiple resections, and multiple enterotomies for removal of meconium, but our efforts have been unsuccessful. Such measure of success as we have had has been achieved only through the rapid and complete relief of obstruction achieved by resection, irrigation and constructed "loop ileostomy."

Postoperatively every effort has been extended toward the rapid restoration of the infant to the point where intestinal continuity may be re-established. TERRAMYCIN® is given routinely as prophylaxis against pulmonary infection. Accurate record of fluid and electrolyte balance is maintained. Daily pancreatin irrigations of the ileostomy are done for the day or two until the child can be given pancreatic extract by mouth, whereupon this is begun. As soon as unequivocal evidence of bowel patency exists, hopefully four or five days, the child is submitted to ileal anastomosis. We have preferred suture to spur crushing for this.

3. Malrotation with obstruction, especially if accompanied by volvulus, calls for immediate surgery. The abdomen should be opened with pause only to transfuse if the child is shocked.

In the presence of midgut volvulus, the bowel will be wound counterclockwise. It must be unwound, and a search then carried out for so-called congenital bands, which will often be found obstructing the duodenum, as they course from the right upper quadrant to the high, left, unrotated cecum.

The hope for cure in the presence of volvulus lies in the early detection of the condition. If gangrene has begun, the prognosis is all but hopeless in view of the large reach of intestine involved.

Obstruction Due to Anorectal Anomalies

Clinical observations and diagnostic procedures—1. Examination of the perineum reveals the anomaly affecting the patency of rectum or anus.

2. Meconium or stool may be observed to issue from urethra, vagina or a fistula opening on the perineum.

3. X-ray study of the abdomen should be carried out. A very useful procedure has been the maneuver described by Wangensteen and Rice.[3] If the child is held in the head-down position, intestinal gas in the rectal pouch will rise to the highest part, in this instance that portion of the rectum closest to the perineum. Using the lateral film, a very accurate estimate of the distance from rectum to perineum may be gathered. The examination is subject to error on two counts. The anterior projection may give an erroneous impression because the child is tilted, and we have limited our measurements to the lateral view, placing a metallic object on the perineum. A second error may be incurred if sufficient time has not been allowed to elapse for air to traverse the colon. This may require as long as 21 to 30 hours.

Synthesis—Complete statistical analyses of the extensive experience at the Boston Children's Hospital have been published by Gross.[2] In addition, his division of these anomalies into four groups has served a useful function in clarifying thinking on the subject. Type 1 is anal stenosis and rarely is a problem in obstruction during the neonatal period. Type 2, the anal membrane, is readily recognized and easily treated. It is type 3, the imperforate anus, with a rectal pouch ending at a varying distance above it, which is at once the most common and also the most demanding of these anomalies. Over 50 per cent of this group have some type of associated fistula. Type 4, rectosigmoid atresia, is really governed by considerations similar to those bearing on the low intestinal atresias. Sigmoidoscopy may, however, be necessary to establish the presence of the imperforate rectosigmoid.

Treatment—When a simple anal membrane has been present, we have preferred excision

and suture of mucosa to skin. This procedure has much to recommend it, is simple, and can be carried out without anesthesia. Stricture following such a procedure is rare.

Where a type 3 anomaly has been present, we have been guided by these principles:

1. If an associated fistula has been present and adequate to permit the passage of feces, surgery has not been carried out in the neonatal period.

2. If the infant weighs less than 6 lb., the perineum has been left inviolate and an abdominal colostomy made. This has been placed in the transverse colon for two reasons: (1) to remove it as far as possible from the site of future surgery and (2) to permit mobilization of as much as possible of the descending colon subsequently, if necessary. Operation is deferred to a convenient time in the preschool age after obstruction has been relieved.

3. If the rectal pouch is within 1.5 to 2 cm. of the perineum, a perineal approach through the sphincter, which is almost always present, may be used. The rectum is mobilized widely and sutured to the perineum, the sphincter being sutured around it.

4. In all cases where the rectum is more than 1.5 to 2 cm. from the perineum, or where the distance remains indeterminate, we have felt it advisable to resist the temptation to exert traction on the rectum after a perineal mobilization, but have extended the benefit of a combined abdominoperineal operation as first described by Rhoads in 1944.[6] The abdomen is entered and the bowel widely mobilized to its distal reaches in the pelvis. Fistulas are divided and repaired. The free rectum is then approached perineally through the sphincter, and repaired. We have shared the agreeable experience of others who have found the abdominal mobilization a simple, effective measure in a newborn infant, provided the child has had the safeguard of an adequate minimum weight to help him through this major surgery.

We have recommended dilatation routinely in *all* cases of imperforate anus. This has been begun approximately 15 days postoperatively, carried out two or three times weekly for one month, and then done at weekly intervals for another month. When rigidity of the perianal tissues has been a matter of concern, the parents have been instructed in digital dilatation and have maintained it for periods afterward. The degree of softening and return of contractility of the anus is always impressive.

Approximately 50 per cent of the patients treated by these methods will achieve a result deemed satisfactory.

Conclusion

An approach to the problem of intestinal obstruction during the first hours of life is discussed. During this period surgery is tolerated well and an opportunity is afforded to extend therapy to infants who have not yet been subject to severe physiologic imbalance.

While they are often disheartened by the hopeless cases of multiple anomalies, surgeons and pediatricians will derive tremendous gratification from the infants restored to health by their astute diagnosis and early therapy.

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The Development of Dramamine®

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MOTION sickness may be described as a physical state that develops in human beings and animals when they are subjected to oscillatory movements over which they have no control. This definition implies that the term should be applied to those symptoms that develop when one is "detached" from the earth, as in a car, plane or ship.

Relatively recent studies of the labyrinth of the ear have elaborated on the earlier classic experiments of Flourens[1] and have crystallized the conclusion that the labyrinth is the most important anatomic area in the causation of motion sickness. The vestibular, or labyrinthine, structures consist of auditory and nonauditory portions. The auditory portion includes the cochlea and perhaps the saccule and the nonauditory portion consists of the semicircular canals and the utricle. Each of the canals found in the petrous part of the temporal bone is paired and forms part of the inner ear.

The bony labyrinth consists of a series of channels which closely approximate the contained soft-tissue structures known as the membranous labyrinth, and these channels are separated from the bony walls by a fluid, the perilymph. The membranous labyrinthine structures are filled with a similar fluid, the endolymph.

The semicircular canals consist of two vertical canals and one external canal to each set. Each canal is curved, each has an expanded portion known as the ampulla, and each communicates at its extremities with the utricle. Furthermore, the nonexpanded portions of the vertical canals join to communicate with the utricle through a common orifice.

The receptor organ of the semicircular canals lies in the ampulla of each canal and is called the crista acustica. Surmounting it is the cupula, a dome-shaped structure consisting of sensory hairs which are free to move in any direction with the flow of endolymph. The detailed anatomy and physiology of the utricle, the cochlea and the saccule can be found in

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the texts of Best and Taylor[2] and of Fulton.[3]

It should be emphasized that the primary function of the semicircular canals is to register changes in the rate of motion acceleration or deceleration and in the direction of motion. Various technics to stimulate the labyrinthine structures have yielded much information concerning this function; for example, rotation of the body, caloric stimulation through syringing the ear with hot or cold water, and galvanic stimulation.

In order to discover possible causes of motion-sickness symptoms and the physiologic site of such disturbances, investigators have attempted to reproduce the symptoms by artificial means. Tyler and Bard[4] carefully combed the literature that pertains to the various studies and have reviewed these investigations.

In February 1949, the preliminary report on the prevention and treatment of motion sickness with dimenhydrinate (DRAMAMINE®) was presented to the Johns Hopkins Medical Society. The study was planned and executed by Gay and Carliner[5] on the U.S.A.T. General Ballou. This transport carried 1,366 soldiers to Bremerhaven, Germany. The data accumulated on this voyage indicated that dimenhydrinate in doses of 50 to 100 mg. every six hours is a nontoxic, prophylactic and therapeutic drug capable of controlling the symptoms of seasickness. The drug was administered orally and rectally, and no untoward side effects were noted by the investigators who accompanied the transport to Germany. In the group of 389 men who developed moderate to violent symptoms of seasickness while en route to Bremerhaven, complete relief was obtained in all but 17 men.

Motion sickness of all types, whether it is produced by sea, car or airplane, is of great interest to a large portion of the world's population. No sex or race is immune. The majority of persons subject to motion sickness recover normal equilibrium within several days after the beginning of a journey; many, however, suffer with motion sickness as long as their feet are off the ground; in fact, some continue to suffer for hours after the motion has ceased.

The rapidity of recovery from seasickness after the use of dimenhydrinate suggests that the perilymph or the endolymph in the semicircular canals plays an important role in the feeling of well-being. Under contract with the Atomic Energy Commission, Haley and Harris[6] published in 1949 a study to determine the extent to which the action of antihistamine drugs is related to a direct effect on the capillaries. These investigators studied the topical application of different antihistamine drugs without either pre- or posthistamine medication with the thought that the site of action of antihistamine compounds might be demonstrated insofar as the capillary bed itself was concerned.

The study covered 27 drugs which were classified as to chemical structure and the effects they produced which divided them into two groups, vasoconstrictors and vasodilators. Diphenhydramine (BENADRYL®) (β-dimethylaminoethyl benzohydryl ether HCl) completely constricts precapillary sphincters, while dimenhydrinate (β-dimethylamino ethyl benzohydryl ether 8-chlorotheophyllinate) does not affect capillaries. This drug dilates the metarterioles and arterioles. The authors explain that the vasodilatation produced by dimenhydrinate (code No. SC-1694), unlike the action of all other so-called antihistamine drugs, probably occurs because the 8-chlorotheophyllinate part of the molecule is more potent than the diphenhydramine part. In particular, dimenhydrinate has a most potent action on the larger vessels in animal subjects.

Adversive Syndrome

A second experimental study on the action of dimenhydrinate has been published by Schiff, Esmond and Himwich[7] of the Medical Division of the Army Chemical Center. These authors reported the correction of forced circling movements (adversive syndrome) by dimenhydrinate. Experimental production of forced circling movements is well known; this reaction can be elicited by means of anatomic lesions applied in numerous areas of the central nervous system. The production of compulsory turning by means of a biochemical lesion was first observed by Freedman and Himwich,[8] who elicited this response by the

intracarotid injection of diisopropyl fluorophosphate (DFP), a drug that destroys cholinesterase and permits accumulation of acetylcholine. They called this response the adversive syndrome. Atropine or scopolamine also corrects this abnormality. It was in an attempt to find another substance which might correct this turning syndrome that the action of dimenhydrinate was investigated.

The adversive syndrome was ". . . brought about by the following method: Under local anesthesia, the common carotid artery of a rabbit was isolated and 0.1 mg. of DFP [per kilogram of body weight] was injected into it. . . . Within a minute or two there was noticed a marked constriction of the pupil on the operated side. . . . Within a few moments the head appeared to be compulsively turned away from the side injected and the chin tended to point slightly upward as though the animal were looking over its shoulder. When the animal was released, it became apparent that compulsive turning movements had completely replaced forward progression. The animal was compelled to pivot on its hind legs or to circle on four legs always in the direction away from the injected side. During this period of active turning the animal was able to maintain its balance and could right itself normally." Blindfolding did not alter the course of the syndrome.

Following the development of the classic adversive syndrome, the investigators gave the animal 5 mg. of dimenhydrinate per kilogram of body weight intravenously. The drug completely corrected the turning effect of the syndrome, and the animal was able to walk straight and to the right and left with ease. When the rabbit was given 10 mg. dimenhydrinate per kilogram of body weight prior to the intracarotid injection of 0.2 mg. of DFP per kilogram of body weight, no turning effect occurred, and the animal was able to walk in a straight line. A lesser degree of miosis on the side injected with DFP was also observed. The authors conclude that dimenhydrinate is capable not only of curing the central vestibular effects of DFP, but also of preventing them. They believe that the drug localizes the effect to central structures and, in the case of the adversive syndrome, to subcorticocerebral areas associated with vestibular functions. They further observe that diphenhydramine, one of the components of dimenhydrinate, produces many similar effects.

Motion Sickness Studies

It is impossible to predict when a traveler will develop motion sickness, even though he maintains that any moving vehicle will produce the unpleasant symptoms. Statistics on prophylactic control of motion sickness are open to criticism, for there are those who might contend that any drug or a placebo will prevent disturbance of equilibrium. Therefore, the following statistics, which supplement the original report of Gay and Carliner,[5] and further findings of Gay,[9] refer to the therapeutic relief of all types of motion sickness—sea, car and air.

Three hundred and twenty-one travelers were treated with dimenhydrinate after motion sickness developed: 210 for seasickness, 52 for airsickness and 59 for car sickness. Of the seasick group 97.1 per cent obtained complete relief from 50 mg. of dimenhydrinate; 1.4 per cent derived partial relief and 1.4 per cent derived no relief. Of the 52 airsick travelers, 98 per cent completely recovered from their symptoms within 15 minutes after taking 50 mg. of dimenhydrinate; 1.9 per cent obtained partial relief. There were no failures in this group. The 59 car-sick travelers responded satisfactorily: 91.5 per cent obtained complete relief; 3.4 per cent obtained partial relief, but 5.0 per cent failed to respond, although they used 50 mg. of the drug. Reactions due to the drug were infrequent. Drowsiness occurred in 11.9 per cent of the 321 travelers, but in no instance was this complaint emphasized in the collected protocols. The dose, 50 mg., was repeated when necessary, but no one required it until four hours after the first dose.

Seasickness

The United States Navy minimizes the frequency of seasickness among its personnel. Nevertheless the navy has taken an active interest in the drug dimenhydrinate.

The report of a project to determine the ef-

fect of dimenhydrinate on marksmanship was published by Shaw.[10] Ninety-six marines were divided into two comparable groups by a random selection as to firing ability and as to positive history of motion sickness. Alternately, on two successive days at four hour intervals, each member of one group was administered 100 mg. of the drug and each member of the other group was administered a placebo. One hour after each administration of the compounds, the groups fired eight rounds slow fire and 32 rounds rapid fire. On the following day the groups were reversed and the procedure was repeated. After a drug-free period of 18 hours, the groups again fired and these results were checked with the experimental study. The conclusion reached by the navy investigators was that dimenhydrinate has no effect on marksmanship.

To study seasickness, these 96 men were then subjected to the motion of the sea in LCVP type landing craft. Alternately, on two successive days, each member of one group was given 100 mg. of the drug and each member of the other group was given a placebo. Thirty minutes after administration the groups boarded the landing craft. After 90 minutes afloat, the boats were returned to the beach, the groups disembarked and fired immediately. Again dimenhydrinate had no effect on marksmanship. Of the 51 subjects to whom the drug was administered, two men (3.9 per cent) manifested signs of seasickness; of the 45 subjects to whom a placebo was administered, 14 men (31.1 per cent) were actively sick. From this pilot experiment, the second conclusion reached by the navy investigators was that dimenhydrinate prevents motion sickness aboard landing craft in a significant percentage of the subjects.

Airsickness

The effectiveness of dimenhydrinate in preventing airsickness was investigated by Strickland and Hahn[11] at the USAF School of Aviation Medicine, Randolph Field, Texas. A procedure was devised whereby one hour flights, simulating flight through turbulent air in a C-47 (DC-3) airplane, were conducted. Volunteers were obtained from the men stationed at the base; no selection factors were utilized; 216 subjects were tested. The drug or a placebo was administered concurrently from 25 to 45 minutes before each flight. Of 108 cadets who were given dimenhydrinate, 28.7 per cent were airsick in comparison with 55.6 per cent of 108 cadets who were given a placebo.

In a subsequent report, Strickland[12] compared the effectiveness of a single dose of 100 mg. dimenhydrinate with a single dose of 0.6 mg. hyoscine, and he reported that hyoscine offers the same degree of protection under similar conditions of acrobatic flight. Medical aspects of passenger flight in commercial airlines have been reported by Lederer, Kidera and Tuttle[13] of Capitol Airlines and United Airlines. As airline medical directors they reported results of an intensive three month study of airsickness among passengers after the administration of dimenhydrinate.

Discomfort studies of passengers who apparently were well have been conducted by each of these airlines. Capitol Airlines carried 1,120,977 passengers during the fiscal year 1946-1947. Among these passengers only 1.16 per cent complained of discomfort and 77.5 per cent of these complaints were because of airsickness.

The report of one month of the three month therapeutic trial made by Capitol Airlines gives the following data: Of 3,528 passengers carried, 270 developed airsickness (7.6 per cent). The most disturbing symptoms of airsickness are sweating, nausea and vomiting. To these patients 50 mg. of dimenhydrinate was administered. Eighty per cent of 155 patients who complained of excessive sweating were completely relieved; 79 per cent of 207 patients who complained of extreme nausea were completely relieved, and 62 per cent of 111 patients who complained of vomiting were completely relieved.

The United Airlines' data are based on a three month study of the therapeutic use of dimenhydrinate. The drug was administered to 1,593 airsick passengers; the dose was 50 mg. The age range of the passengers was from 10 years to over 60 years, with the majority from 21 to 60 years of age. The therapeutic administration of the drug to the 1,593 pa-

tients gave the following results: 16 per cent continued to vomit and to complain of nausea and dizziness; 29 per cent improved and nausea and vomiting ceased; 55 per cent obtained complete relief of all symptoms. As in seasickness, the majority of these persons responded to the drug within 15 minutes.

Labyrinth Disturbance

The control of labyrinth disturbance has been difficult. Many remedies have been tried, and many failures have been encountered in spite of variations in treatment. The reaction of the labyrinth to the fenestration operation offered an opportunity to use dimenhydrinate. Campbell[14] reported these results when he used the drug following labyrinth fenestration on 28 patients. The average patient vomits frequently throughout the day of operation and always when aroused or disturbed in any way. The patient is unable to retain liquids, and it is the general policy to give him 2000 cc. of a solution of glucose and saline during the 10 hours after operation. It is quite common for patients to vomit 10 to 12 times within the first 24 hours. On the day after operation, the average patient has considerable vertigo and much nausea, and he vomits from two to six times. Nystagmus on the day after operation is usually so severe that the patient is unable to raise his head or to have the bed elevated. On the second day after the operation, the average patient can take liquid diet but he still has much vertigo and nausea and frequently some vomiting. On the third day the patient is able to have the head of the bed elevated, he can be put on a soft diet, and, except for the occasional patient, he does not vomit. On the fourth day after the operation, the patient is able to get out of bed. Although he experiences a severe sense of unbalance, this gradually passes the next day or two.

Dimenhydrinate (100 mg. tablet) was administered by mouth, except to a few patients who had vomited the first dose and to whom the drug was then given by rectum. The general plan was to administer 200 mg. immediately after the patient returned to his bed from the operating room and to administer subsequent doses (100 mg. each) at three hour intervals for four times—a total of 600 mg. on the day of operation. On the second day a 100 mg. dose was given every three hours for six doses. The drug was not administered on the third or on subsequent days unless vertigo became worse. This occurred in a few instances. The postoperative care of the 28 patients who were given dimenhydrinate was exactly the same as that given the numerous patients who had been operated on previously and whose reactions served as a standard for comparison. Campbell reported the following results after the administration of the drug:

After operation there was only slight nausea with no vomiting. In all of the 28 patients, the vertigo was moderately to markedly relieved. A surprising feature was that only a few of the 28 patients relapsed after the drug was omitted. Prompt beneficial effect was particularly noticeable in those patients who showed relapses. The treated patients were able to enjoy a normal diet approximately two days sooner than untreated patients, and were able to be discharged from the hospital one or two days earlier.

The pharmacology and toxicology of dimenhydrinate have been examined in the laboratory of the manufacturer. The data published in the original observation by Gay and Carliner[5] indicated that oral administration of the drug in doses of 50 to 100 mg., every four hours for a period of from 6 to 10 days, provides an ample margin of safety. Subsequent collection of an even larger number of protocols by the authors has confirmed this observation. Personal experience suggests that robust, healthy soldiers and sailors have a higher tolerance for a 100 mg. dose administered every four hours than have persons in everyday life. In many instances the 100 mg. dose causes drowsiness, but a dose of 25 to 50 mg. subsequently given to the same individual has no unpleasant reaction, yet relieves or prevents the symptoms. The initial administration of 25 to 50 mg. should gauge the next dose. Reports accumulated from other observers of the action of dimenhydrinate have emphasized that a dose of 100 mg. may cause a subjective sensation of muscle tremor in the extremities.

Following the original observation by Gay and Carliner[5] that dimenhydrinate prevents motion sickness in the majority of susceptible travelers, Gay treated 63 patients suffering from acute or chronic labyrinthine symptoms. Their ages ranged from 16 to 74 years. The average dose of dimenhydrinate was 50 to 100 mg. every four hours; the majority of the patients took the drug for at least seven months.

The 63 patients were separated into three groups. In group 1 were six patients who were seen within three weeks after the onset of dizziness, nausea and vomiting. In group 2 were 41 patients who had had dizziness, nausea and vomiting for periods varying from two months to 25 years. All these patients either were cured completely or had only infrequent and minor attacks as long as they continued to take dimenhydrinate. In group 3 were 16 patients with symptoms similar to those in group 2; all failed to respond to dimenhydrinate. In fact, in five patients the dizziness became more pronounced after 100 mg. of the drug had been taken. The dizziness, nausea and vomiting were so severe in four of the patients that the vestibular nerve was sectioned intracranially with no relief. Dimenhydrinate, administered in doses of 400 to 600 mg. a day, failed to give the slightest relief. No explanation is offered for these 16 failures. In this report 74.6 per cent of the 63 patients with imbalance were greatly improved after taking the drug. Many of the patients had to continue maintenance doses to remain free from dizziness. This report has been added since it demonstrates the possible site of the action of such drugs as dimenhydrinate prescribed to persons susceptible to motion sickness.

Summary

Therapeutic trials have demonstrated the great relief which seasick, car sick and airsick travelers obtain if they take 50 to 100 mg. of dimenhydrinate after the onset of symptoms. Unlike any drug heretofore reported as a remedy for motion sickness, dimenhydrinate can be taken in proper doses by the majority of travelers for an indefinite number of days with no unpleasant symptoms. Controlled prophylactic trials previously reported by Gay and Carliner[5] have been just as successful when the drug was administered 15 minutes prior to departure of a ship, car or plane.

The efficacy of dimenhydrinate in labyrinthine disturbance following fenestration has been demonstrated by Campbell.[14] This report also presents the results obtained by the administration of dimenhydrinate (50 to 100 mg. every four hours) to patients with various types of dizziness, of labyrinthine as well as of central origin. The benefits these patients derived from the drug show that dimenhydrinate should be given to all patients with disturbance of balance before they resort to section of the nerve by the neurosurgeon, or to the destruction of the labyrinth with alcohol injection, or to electrocoagulation performed by the otologist.

Although the physiologic action of the drug is not certain, the evidence available suggests a central action; other investigators suggest from their research that the benefit from the drug points to local action on the blood vessels and on the labyrinth.

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Art Exhibit

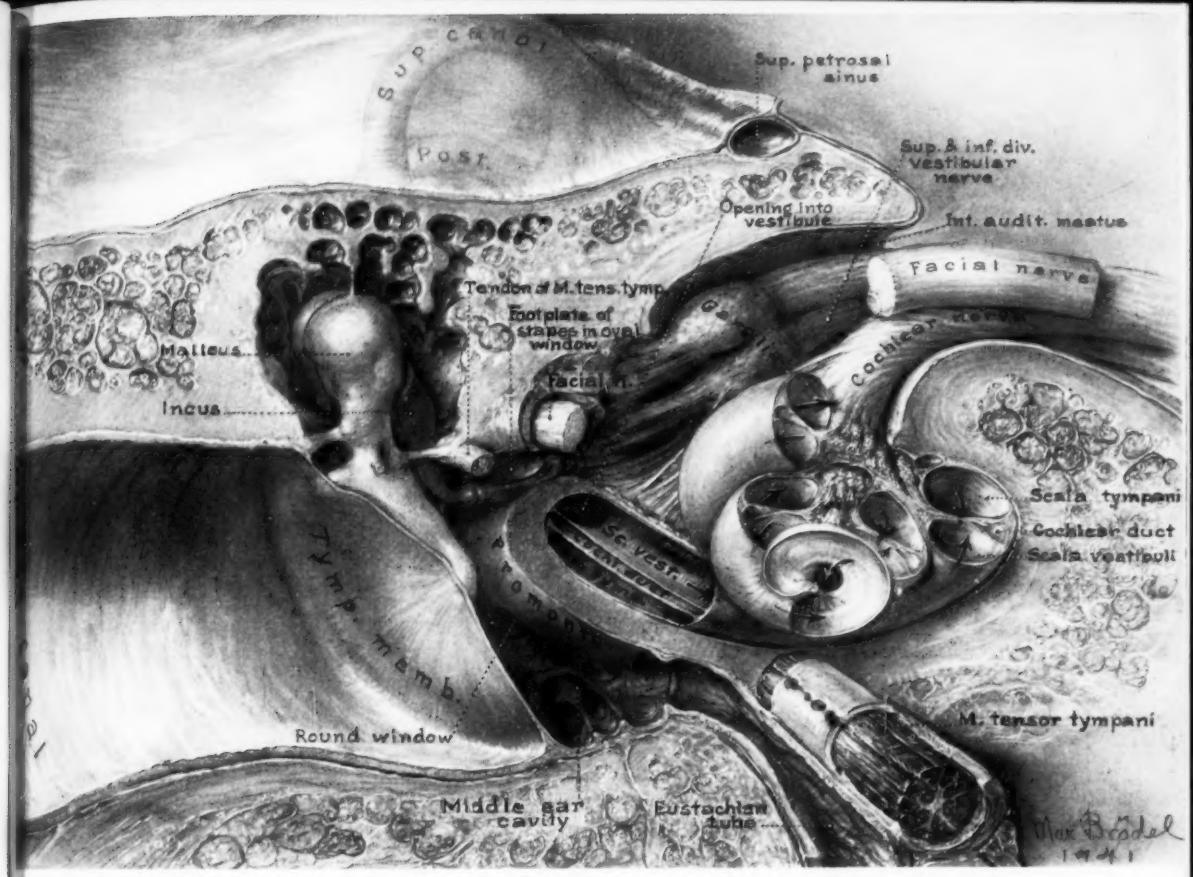
MAX BROEDEL

Max Broedel was born in Leipzig, Germany, on June 8, 1870. He studied at the Leipzig Academy of Fine Arts from 1884 to 1890, and was employed by Professors Karl Ludwig and Wilhelm Braune of the Physiological and Anatomical Institutes to make drawings of the heart and large topographic anatomy charts and some illustrations of laboratory experiments. It was here that he met Dr. Franklin A. Mall and Dr. William H. Welch, professors of anatomy and of pathology of the newly formed Johns Hopkins Medical School. On the recommendation of the former, Max Broedel came to Baltimore in 1894 to prepare medical illustrations for Dr. Howard H. Kelly's book, "Operative Gynecology." He worked for Dr. Kelly and his successor, Dr. Thomas B. Cullen, for the next 17 years.

While doing this work he was borrowed by men in other departments of the medical school and hospital. The excellence of his work led to the establishment of a Department of Art as Applied to Medicine in 1911, through the efforts of Dr. Cullen and the endowment of Mr. Henry Walters, a Baltimore businessman and philanthropist. Here he remained until his death on October 26, 1941. Thus, he spent 47 productive years revolutionizing medical illustration.

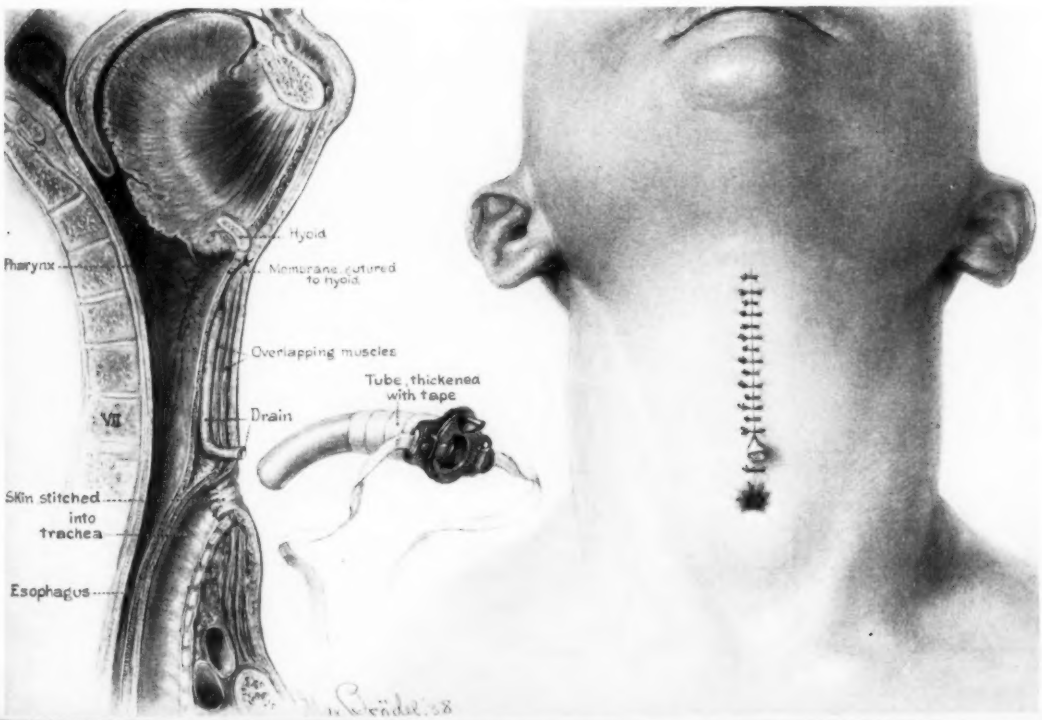
At the time Max Broedel left Germany medical illustrations were being made in elaborate and time-consuming media: lead pencil, water color and oil paint. Realizing that a swifter technic meant a more artistic picture he experimented with different papers, finally selecting one coated with chalk and having a stippled surface. Spontaneity of sketching and saving of tracing time were effected by a unique transfer system of the final sketch onto this paper. The use of carbon dust with a dry brush on stipple board lends itself to all kinds of texture representations. High lights, indicating the glistening character of fresh tissue, are lifted out of the chalk with erasers and a metal scraper. This halftone medium is now referred to as the "Broedel technic."

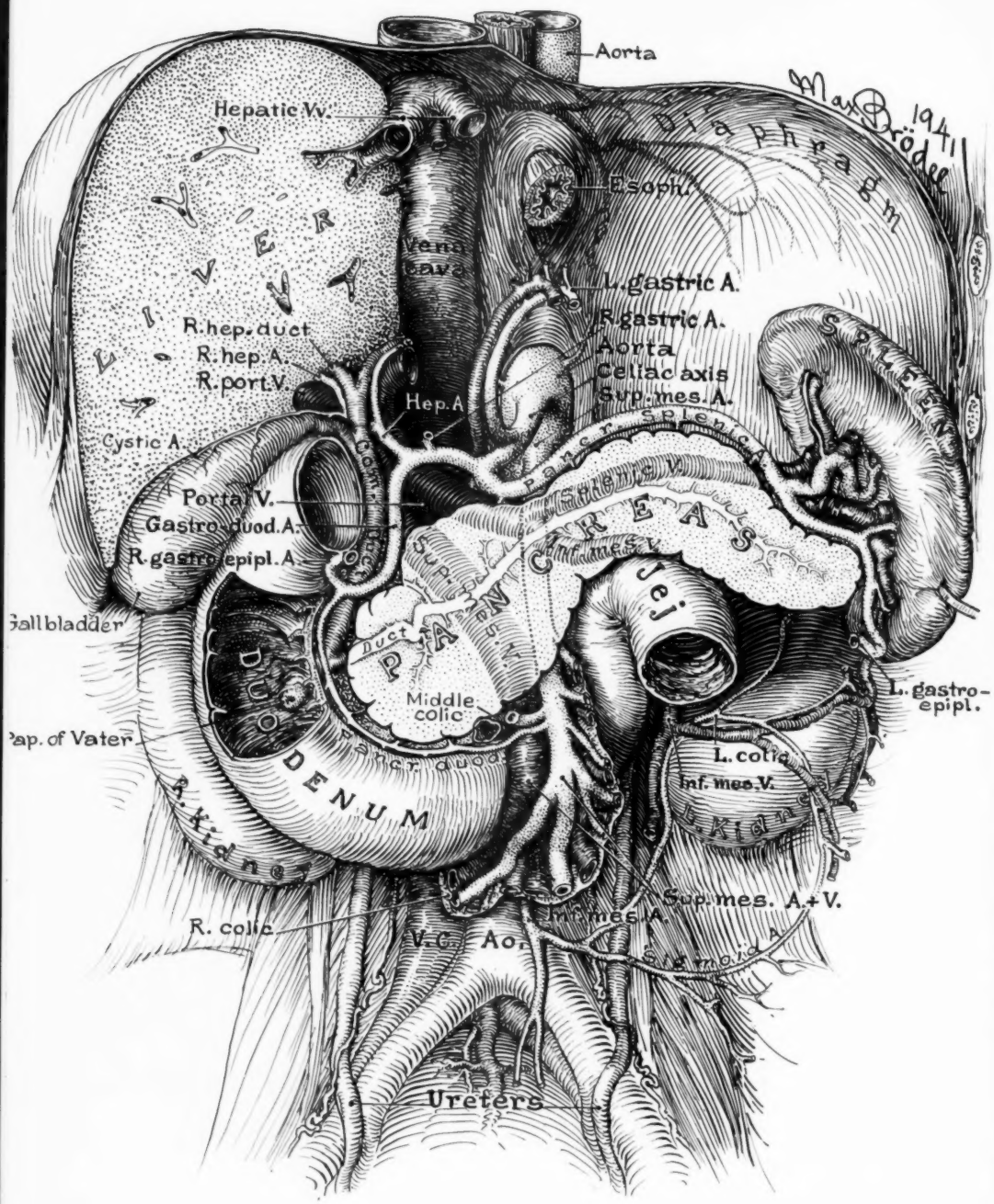
Max Broedel's many pupils have become distinguished illustrators in their own rights. Following are a few examples of his work and of theirs. These latter in their special fields include: William Didusch, urology; Annette Smith Burgess, ophthalmology; Leon Schlossberg, cardiovascular and general surgery; and Ranice Birch Davis, obstetrics. Mrs. Davis has succeeded Mr. Broedel as Director of the Department of Art as Applied to Medicine.



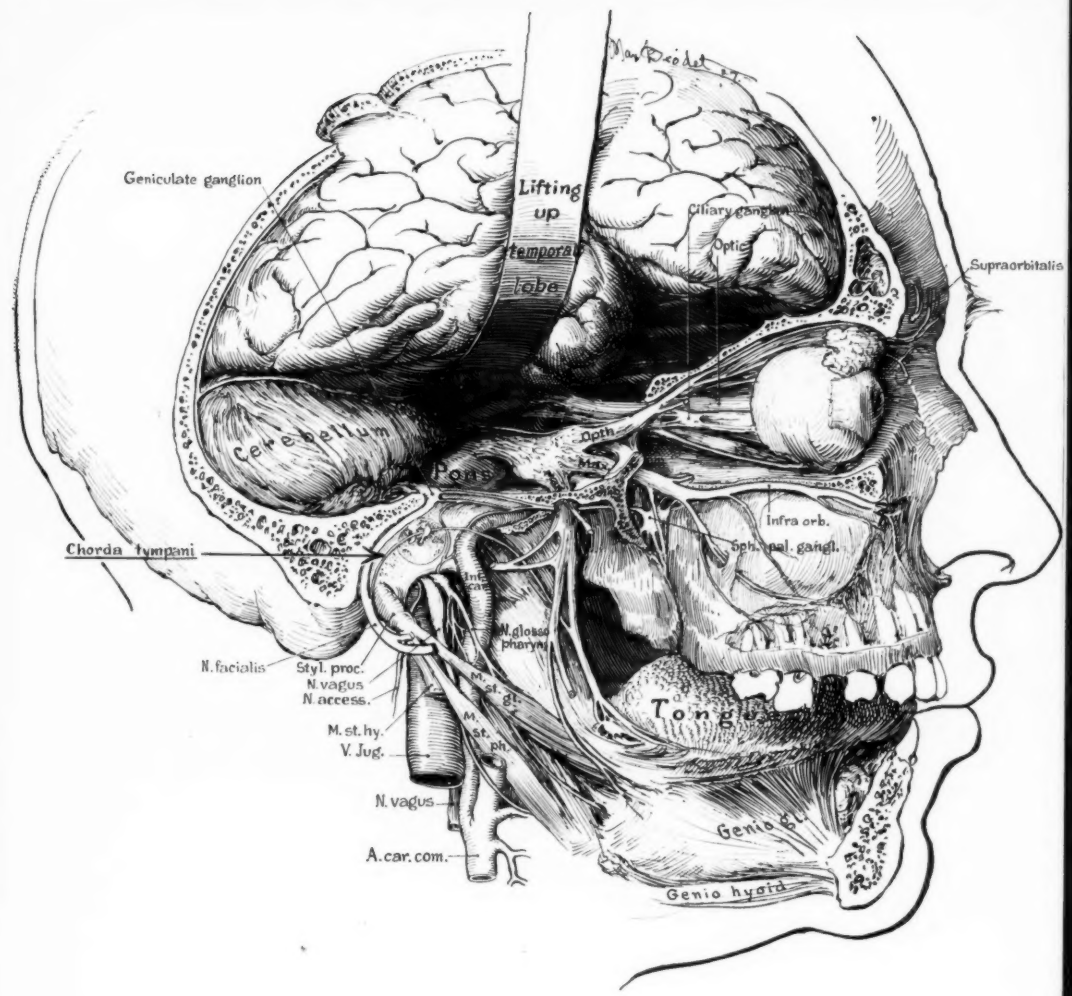
Anatomy of the human ear. By Max Broedel.

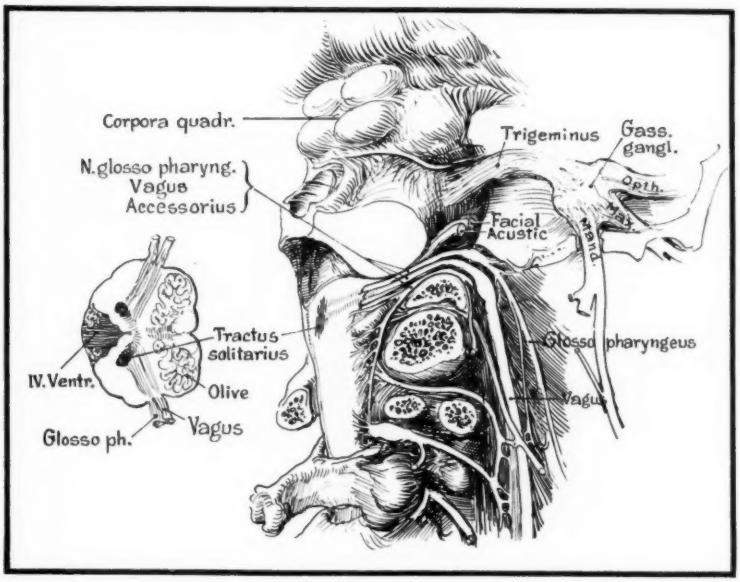
Carcinoma of the larynx. Wound closure and eventual withdrawal of rubber tissue drain. By Max Broedel.



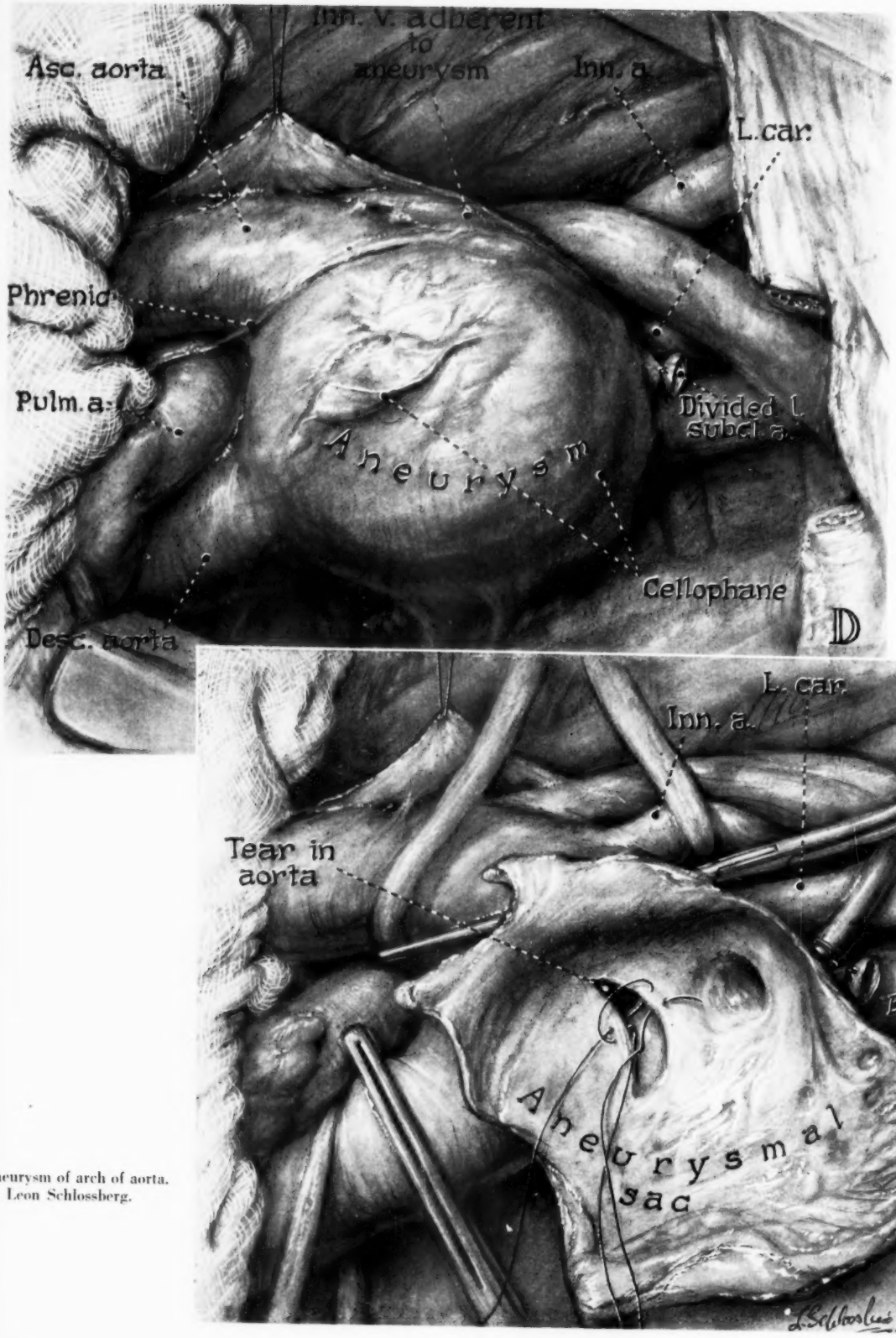


Normal topography of the upper abdomen. By Max Broedel.



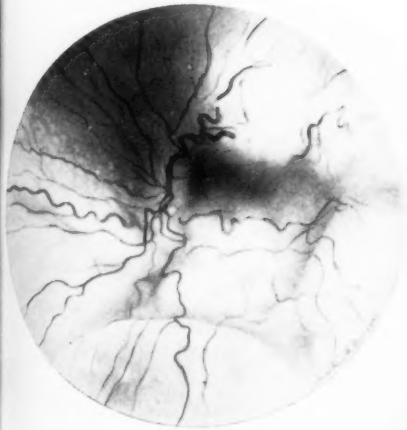


Taste fibers of the tongue.
By Max Broedel.



Aneurysm of arch of aorta.
By Leon Schlossberg.

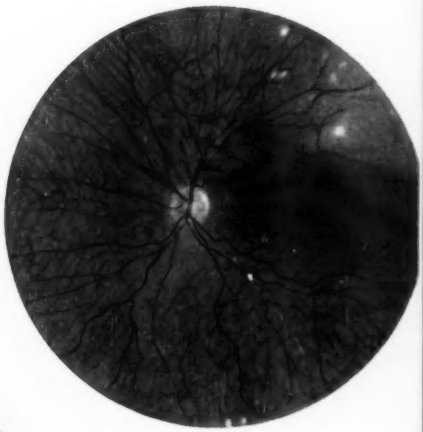
Left. Low cervical cesarean section. *Right.* Horizontal incision with manual delivery of infant's head. By Ranice Birch Davis.



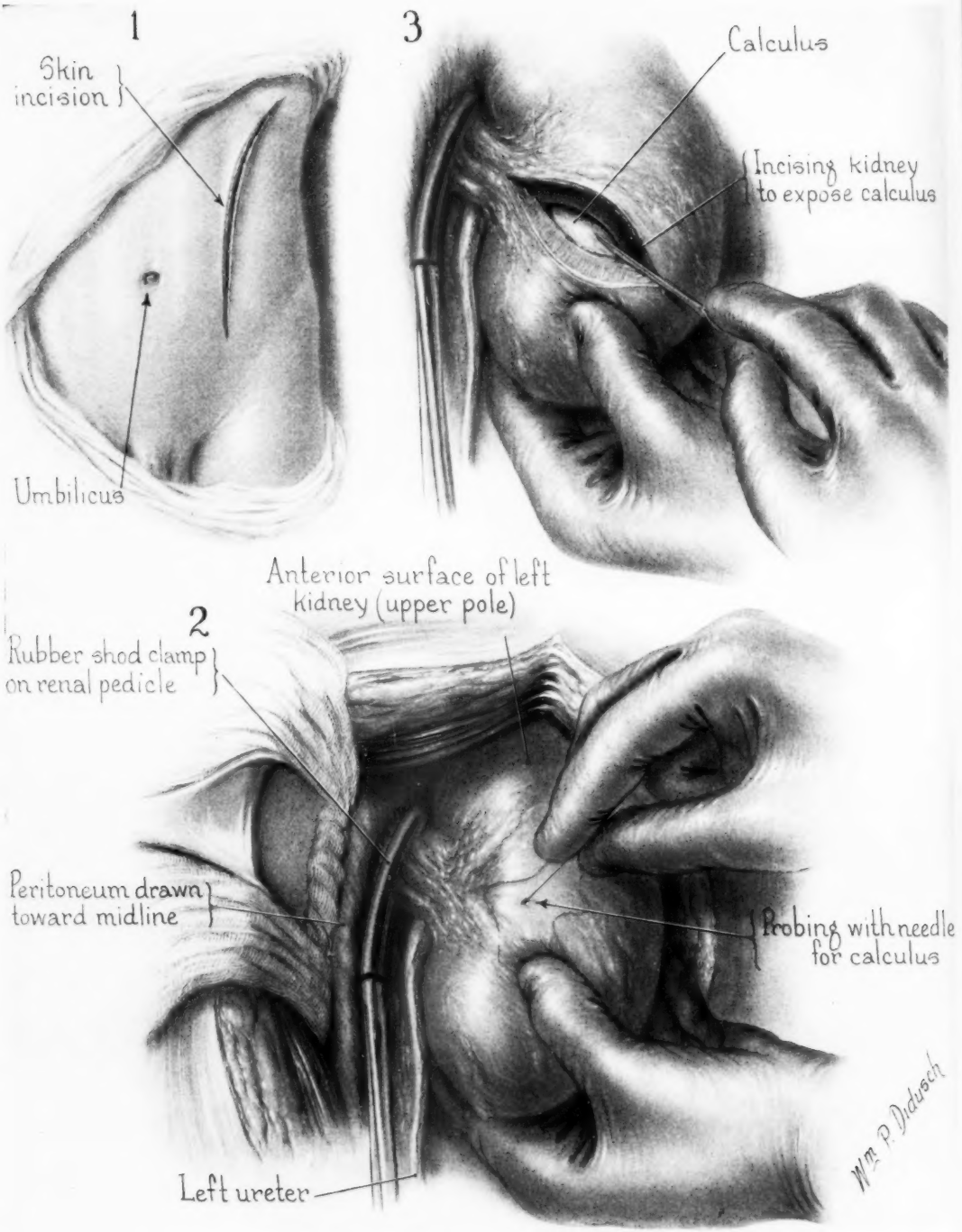
1. Before therapy.

Retinoblastoma before, during and after therapy with intravenous nitrogen mustard. By Annette S. Burgess.

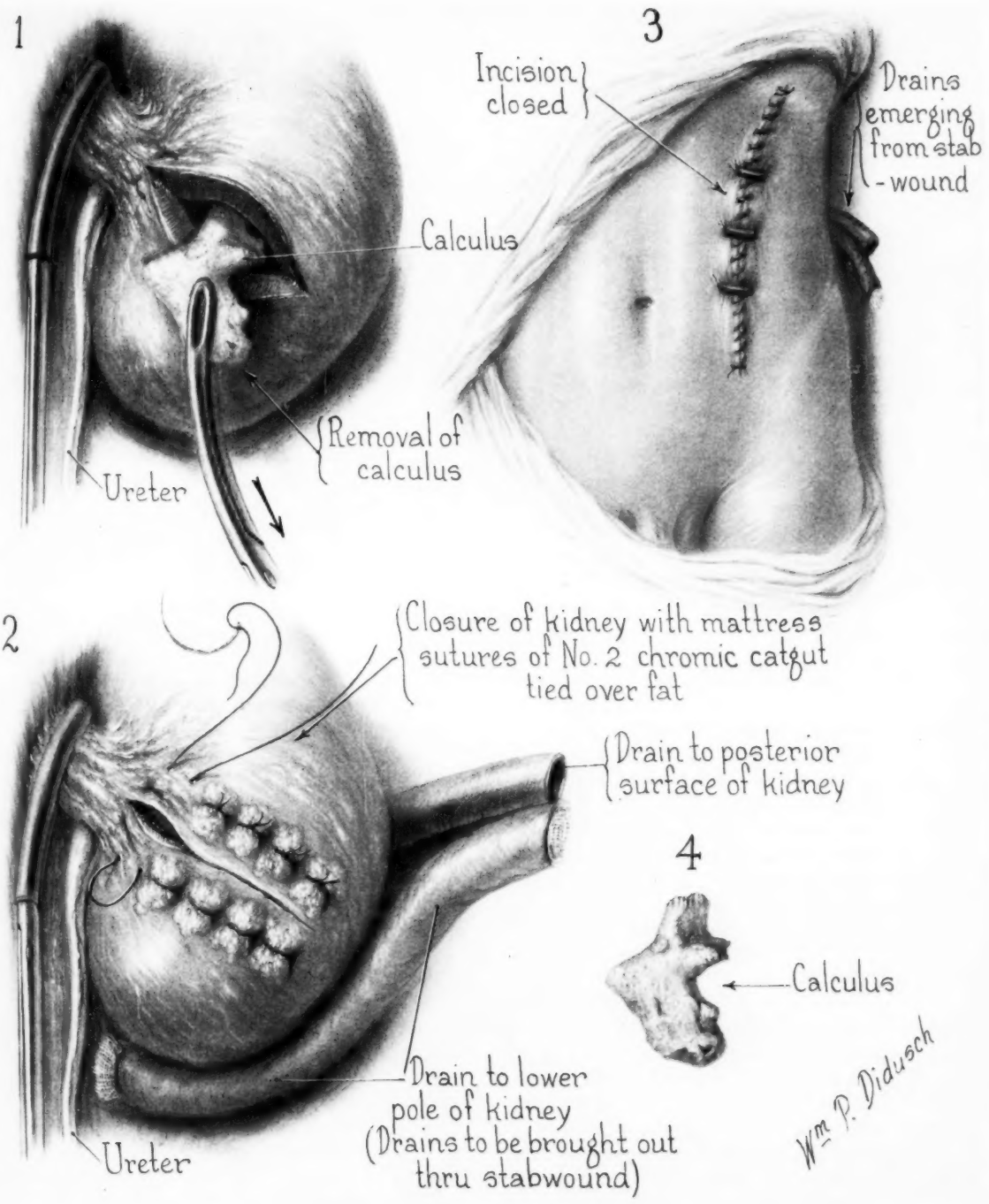
2. Fourteen days after therapy.



3. Fifty days after therapy.



Nephrolithotomy No. 1. By William P. Didusch.



Nephrolithotomy No. 2. By William P. Didusch.

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HOPKINS RESIDENCY TRAINING SYSTEM

THE residency system of training was born at The Johns Hopkins Hospital under its first professor of surgery, William Stewart Halsted. Its adoption by other departments of medicine in this country and elsewhere came slowly, but now the system is recognized as probably the chief contribution of this institution to surgical and medical training throughout the world. A natural development of this system has been the encouragement given to *young* men to work in the hospital and medical school and to compete on an equal basis with all senior men on the staff.

In 1935, soon after I had finished seven years on the resident surgical service at this hospital, and before the days when the residency system had been generally adopted elsewhere, and before the days of American Boards examinations, I wrote briefly of my ideas of this system. These ideas were never before submitted for publication, but because they seem to be as true today as they were in 1935, and because I believe they will still be true in 2035, I am offering them here.

Too often the young surgeon is given the wrong approach during his training period. The hospital apprenticeship, when he should work under fully trained superiors, is inadequate; and every year many hundreds of men are turned loose to practice surgery after but a year or two of internship, perhaps supplemented by some assisting in the operating room or, possibly, by the actual performance of a few "major" operations.

Sufficient training for a man to practice properly is of necessity long. After a medical degree has been obtained there is still the period of apprenticeship before the proper judgment and technical ability have been gained to enable one to perform surgical operations with safety. Only experience under careful guidance can give this ability and this judgment—and these should be gained not at the cost of injury and death of patients treated by an inadequately trained surgeon, but through a long period of apprenticeship characterized by assisting experienced surgeons

and performing operations of gradually increased magnitude, supervised by these experienced surgeons.

Strategy in attacking a surgical problem may be worked out excellently in advance, but unless the surgeon's tactics in the actual field of operation are proper, he will readily defeat his purpose. When different surgeons perform operations which are in principle exactly the same, some of the patients will recover rapidly and permanently; others will be subjected to operative shock, hemorrhage, infected wounds, unphysiologic results and death. The question arises of why one surgeon almost invariably operates with favorable results and another surgeon experiences so much difficulty—when apparently the operations are exactly similar. Certain variable factors which are responsible for this difference are obvious: the patient's physical condition, choice of time for operation, type of anesthesia, type of operation, knowledge of anatomy, and attention to operative detail.

In a few months' time a man may acquire sufficient knowledge to remove a relatively uncomplicated appendix, uterus or gallbladder, but, when these organs are found at operation to be more seriously involved, it is then that patients will be sacrified by the inadequately trained surgeon. Only a long period observing the work of superiors—during which time the apprentice surgeon first performs minor operations repeatedly and then adds to his repertoire the more difficult operations—will give the proper approach to surgery, a way that often may seem the unnecessary repetition of dull routine.

A fact not generally appreciated is that the bulk of an apprentice surgeon's training does not come from the men on the visiting staff but from his immediate superiors on the resident staff. Theirs is the stable bureaucracy that carries on from day to day and year to year and transmits the surgical principles of that particular hospital to succeeding groups of house officers. That is why surgical training services of one, two or even three years' duration almost invariably fail to train a man properly; that time is too short to build up a continuity of training that will pass along automatically to those who follow.

The nature of the material on which the surgeon exercises his handicraft is too precious to be subjected to the insult of a hastily and inadequately trained man. Such a man will never acquire the correct attitude no matter how frequently he may operate. His patients will experience a stormy and adventurous course, because in his formative surgical days he did not travel the avenue of the correct approach. He may learn to operate rapidly and acquire a certain technical skill, but even this advance will be limited and of little avail in the absence of proper diagnostic acumen, a solicitous method of attack, the requisite operative judgment, and the detailed care and finesse of a properly trained surgeon.

In the days when anesthesia was badly regulated, the preoperative and operative care of the patient insufficient, and hemorrhage ill-controlled, everything was sacrificed for speed. A popular slogan was that of the late John B. Murphy, of Chicago, to "Get in quick and get out quicker." The quoted words in the next few paragraphs are from the remarks made by Dr. Rudolph Matas at a commemorative meeting held for Dr. Halsted soon after his death.

"Happily for us and for humanity, the time has long passed when surgical brilliancy and ability could be gauged by the clock, or when the relative merits of surgeons could be estimated by the rules of the prize ring or the authority of the Marquis of Queensberry. That was well enough in the dim days of antiquity, in the days of Galen and Celsus, when limbs of conscious men were amputated with an axe or a guillotine; or in much later days, when a Lisfranc, a Dieffenbach, a Lizars, or a Liston could disarticulate a hip in five minutes or less, provided that in the flourish of blades, one or more of the assistants were not put *hors de combat* by the lightning maneuvers of the operator; or that one could say of a modern master what was said of Fergusson, who, in lithotomy, proceeded with such lightning speed and skill that someone advised a prospective visitor to his clinic to, 'Look out sharp, for if you only wink you will miss the operation altogether!'

"Then, time was everything, and any procedure that would relieve the patient of his encumbrance by the shortest route was at the highest premium. Before the discovery of anesthesia, the surgeon had to be a man with a heart of steel in order to carry on his work of relief in an atmosphere reverberating with shrieks and yells, lurid with blood, and laden with the germs of disease and death. Then indeed, he was the best surgeon who could slash off an offending limb in the quickest time. Then, indeed, brilliancy consisted in speed, speed at any cost, and the price of speed was high. As late as the nineteenth century, the death rate was enormous, full 95 per cent and over for the hip; 70 to 80 per cent for the thigh, and so on. At present, by the modern methods of safety, it has fallen to an insignificant and negligible figure, in so far as the operative act is concerned. However, do not misunderstand me as depreciating the quality of speed when this is not a mere race for a record but is the legitimate outcome of dexterity, knowledge, system and method; the outcome of long experience and faithful practice in surgical exercises.

"But, I do not reckon speed as brilliancy when displayed chiefly, if not solely, for spectacular effect; when it is exhibited at the expense of security, and when appraised as skill it is rated above caution and judgment at the hazard of the patient's highest interests.

"The brilliancy of the operator should not be appraised by the time he consumes in the performance of an operation, but by the effect that follows its achievement; not in the mere recovery of the patient from the immediate operative act, but in the way in which he recuperates; in the length of time required for his recovery; in the period demanded to restore him to usefulness, and, above all, in the permanency of the cure which it accomplishes.

"It is in this manner that I would rate and compare the brilliancy of surgeons, and it is from this viewpoint that Halsted is considered one of the most brilliant and greatest surgeons of his time. It is the sort of brilliancy at which he aimed and with which he sought to imbue his pupils through his teachings and example. It is the sort of brilliancy for which every conscientious surgeon, who places his patient's welfare and the good repute of his profession above the vanity of his own flesh, should strive."

Unfortunately, this view, so well expressed by Dr. Matas, that the brilliance of an operator be gauged by his speed and manual dexterity, is still held by many except the most competent critics—experienced colleagues—who know that the brilliant surgeon is one who heeds not the applause of the gallery but the dictates of his own conscience, and whose patients, therefore, recover most often, most rapidly, and with the best physiologic results.

Finally, the words of Marshal Foch should be borne in mind when he said, "Experience alone can develop judgment, and the habit of authority, which alone can ensure to an officer the calm confidence which leads to wise as well as vigorous decision."

I. RIDGEWAY TRIMBLE

MEDICINE 1955

THE most exciting announcements of medical progress in the year just passed included the establishment of the Salk vaccine against poliomyelitis, the development of the ataractic agents which produce freedom from confusion and peace of mind, the appearance of several new antibiotics with remarkable properties, and the report from Germany of a new substance to be taken by mouth for control of blood sugar.

During this year also prednisone was developed as a product preferable to cortisone for many conditions. Our knowledge of surgery of the heart advanced so that all four valves have been approached surgically. Such extraordinary observations have been made as the fact that scabies is gradually disappearing as a disease. New anticonvulsants and antispasmodics are effecting benefit in the treatment of Parkinson's disease and epilepsy. The mechanism of heartburn is better understood. The location of tumors of the brain through the use of radioactive substances reached an efficiency of some 75 per cent. A tryptic agent was applied and caused the early disappearance of "black eye." A dye substance was developed which when swallowed in tablet form gave indication of presence or absence of free acid in the stomach, eliminating the use of the stomach tube for this purpose.

On April 12, 1955, at a special meeting in Ann Arbor, Michigan, under the auspices of the University of Michigan, Dr. Thomas Francis announced the results of the greatest controlled experiment performed in the history of medicine. The experiment showed the effectiveness of the Salk vaccine against poliomyelitis. The United States Public Health Service released the vaccine as manufactured by six manufacturers for general use and the National Foundation for Infantile Paralysis prepared to inoculate all children in the sixth and seventh years of age with two doses of the vaccine given 10 days apart. A third dose was to follow after 10 months as a booster dose to give the greatest possible and longest lasting immunity. Unfortunately one of the vaccines contained living virus and many children developed acute paralytic poliomyelitis as a result of inoculation with this vaccine. Subsequent plans were made to change the system of inspection, leading toward maximum safety. As the year ended, announcement came from the United States Public Health Service that even one dose of the vaccine may yield high immunity, that inoculation is safe and effective, and the outlook is bright for ultimate disappearance of paralytic poliomyelitis as a constant and imminent threat in the United States.

Ataractic Agents

People live at a speeded-up rate and multiple tensions bear constantly on the human being. Tranquilizing substances now begin to appear in several forms. Most notable among those previously known were rauwolfia and chlorpromazine. Today these drugs are being used widely in the treatment of various mental disorders and they have revolutionized the conduct of institutions for the mentally disturbed. Many different preparations of rauwolfia and of reserpine are offered by the manufacturers. A new product Frenquel is the gamma isomer MERATRAN®. The mechanism of action of these products is not established or fully understood. Apparently they are concerned in the development of serotonin in the brain. Among the other drugs which depress the action of the nervous system are MILTOWN® which is known also as EQUANIL®, and the longer-established mephenesin. FLAXEDIL®, which is gallamine triethiodide, and mephenesin, which is sold under a great variety of names, are in the general group of relaxants of the skeletal muscles. They provide more complete muscular relaxation during such procedures as anesthesia, manipulations, the use of the gastroscope and the application of intubation. These drugs have contributed greatly to the progress of diagnosis and therapy. They have great power but their use is associated with some danger. Another skeletal-muscle relaxant is succinylcholine chloride which is a blocking agent that acts at the nerve-muscle junction. Miltown—meprobamate—is relatively nontoxic and seems to be of use chiefly in treatment of

anxiety syndromes and of tension states.

Various combinations of these preparations with sedatives of the barbituric acid type have yielded encouraging results beyond anything that could have been anticipated a few years ago. They have been used widely in the treatment of hypertension, particularly of the type associated with anxiety and stress. For instance, Miltown, which, incidentally, was named for the place in New Jersey where it was discovered, has proved effective as a tranquilizing agent in anxiety and tension states, for inducing natural sleep, as a muscle relaxant, for relief of muscle spasm, for control of spasticity, for alcoholism, and for certain convulsive disorders. The drug does not knock patients out but calms them by blocking conductivity in the interneuronal circuit.

Incidentally two drugs—mescaline and LSD, which is a product of d-lysergic acid—are being extensively used in experimentation to determine the mechanisms of such conditions as schizophrenia. Important studies with the latter drug began as far back as 1943. Many experiments have been done on human beings with these hallucinogenic agents. Glutamic acid can interrupt or retard the effects of LSD. In acute schizophrenics the symptoms caused by LSD are an exaggeration of symptoms that already exist. Chronic schizophrenics exhibit behavior like that in acute episodes. Schizoid patients with depression complain of an intensification of anxiety, depression and physical symptoms. Investigators in the National Institute of Mental Health conclude that LSD makes it impossible for the ego to integrate the evidence of its senses and to coordinate its activities. Through studies of this type scientists are coming closer to an understanding of the nature of schizophrenia.

Epilepsy, Myasthenia Gravis, Parkinsonism

Two new preparations are now available in the treatment of epilepsy and seem to be having general acceptance. These are MYSOLINE® which is used preferably in grand mal and MILONTIN® for petit mal.

In myasthenia gravis a new drug is Mysuran chloride and the clinical reports seem to give it advantages over other drugs previously used, as, for instance, neostigmine. The chief advantage of some of the newer drugs is that they offer a lessened toxicity.

Two new drugs have been developed for the treatment of parkinsonism. These are Kemadrin and Parsidol. Clinical studies have shown that these have greater effectiveness than ARTANE® and PAGITANE®, previously used, and perhaps with less toxicity. Both drugs apparently decrease tremor and rigidity.

BZ-55 for Diabetes

In October German investigators made available the results of research with a new sulfonamide substance that definitely lowers blood sugar through action on the pancreas. The substance is called thus far BZ-55. This substance is rapidly absorbed when taken by mouth and apparently acts to stimulate certain cells of the pancreas in such a manner that they interfere with the glucogen produced by the A cells of the pancreas and known to be antagonistic to insulin. When this interference is ended, more insulin is produced and as a result the sugar is lowered. The substance is still in an experimental stage. When tried on normal persons it produced fatigue, sweating, hunger and tremor with euphoria, which might be considered excess insulin effects. Comparison is made of this product with DIAMOX® which is also a sulfonamide derivative and which acts to block enzymes—namely, carboanhydrase—and thus produces greater activity in the kidney.

Infections

Information was developed by research carried on in the armed forces that infectious mononucleosis is transmitted principally by kissing. Conclusive studies were made during an outbreak of this condition which took place in an armed forces barracks. Apparently the condition did not spread from one person to another within the barracks but instead was spread through contact of persons in the barracks with the same person of the opposite sex outside.

A substance called properdine found in blood plasma combined in the presence of

magnesium with a carbohydrate in the walls of bacterial cells. Thus properdine is a constituent necessary to building resistance to infection in the blood. It acts to prepare the bacterial cells which may enter the blood in such a way that they can be affected by an enzyme in the plasma which destroys foreign substances. The investigators reported that exposure of animals to exceedingly large amounts of irradiation decreased the amount of properdine in the blood and thus interfered with the ability of the animals tested to resist infection.

A survey made in New York indicated that the increase of the Puerto Rican population of that city has resulted in a greater incidence of schistosomiasis. The condition previously has never been seen with any frequency in the United States, although it is not unusual in Puerto Rico.

Diseases of the Skin

While research is still trying to find specific methods for treating such conditions as psoriasis and the mycotic diseases which seem to be spreading, two of the conditions long listed as among the first 10—namely, eczema and scabies—are disappearing rapidly from specialistic practice. Eczemas are being treated with ointments of cortisone and the response has been so prompt and successful that the condition is being cared for primarily by general practitioners. Cortisone and its derivatives are also used for ivy poisoning, drug eruptions, urticaria and erythema multiforme as well as in long-continued conditions such as lupus erythematosus and pemphigus.

Surveys indicate that scabies is becoming practically nonexistent in North America, Europe and in some of the Pacific area; the reason for the infrequency of the condition has not been determined but it is believed to be related to the introduction of better laundering involving the use of detergents and washing machines.

Research is continuing on the cause and treatment of various conditions involving pigmentation or its lack in the skin. The hormone from the pituitary known as MSH, or the melanocyte-stimulating hormone, is being investigated. Drugs, as previously mentioned, derived from the Egyptian Ammi majus are found effective when combined with exposure to ultraviolet in relieving vitiligo in many cases. To produce depigmentation a substance called BENZOQUIN® is undergoing testing.

Rheumatic Fever

Extensive studies have established the possibility of reduction in the incidence and the number of relapses in rheumatic fever by proper and effective treatment of streptococcal infections of the throat. The drugs used have included the newer antibiotics such as erythromycin, and chief reliance has been placed on penicillin and sulfadiazine. Other preparations used have included oxytetracycline (TERRAMYCIN®), also BICILLIN® and AUREOMYCIN®. A single injection of approximately 1,000,000 units of a repository preparation, benzathine penicillin, has also been reported extremely effective. Especially important is considered to be the prompt diagnosis of streptococcal sore throat which is usually accompanied by sudden onset of fever, extreme redness of the pharynx with soreness, inflammation of the glands, and increase in the leukocytes. Obviously distinction must be made between this condition and the usual cough, cold, hoarseness or allergic condition.

Prednisone and Prednisolone

Among the most significant developments of 1955 was the introduction of products now generally known as prednisone and prednisolone under a variety of names, such as METICORTEN®, METANDRASEN® and METICORTANDROLONE®, also STERANE®, DELTACORTRIL®, DELTASONE® and DELTA-CORTIF®, also DELTRA® and HYDELTRA®. The advantages over cortisone and hydrocortisone consist in the increased potency of these preparations and in the fact that they do not interfere with the salt and water metabolism. In some instances patients who have seemed to cease to benefit after prolonged treatment with cortisone and hydrocortisone developed favorable reactions with the new drugs. A difficulty is the increased hydrochloric acid that sometimes develops in the stomach in connection with the use of these preparations and in the increased

incidence of ulcer. The drugs have been given extended trial in rheumatoid arthritis, in cases of intractable bronchial asthma, and in most of the other conditions for which cortisone and hydrocortisone have been found useful. In the treatment of rheumatic fever and in various blood dyscrasias, the new preparations serve equally as well or better than the older ones.

Incidentally cortisone has been found by some investigators to yield favorable effects in cerebral hemorrhage. Its use in ulcerative colitis has been previously mentioned and is now being extended. In Great Britain a report of the British Medical Research Council concluded that patients with acquired hemolytic anemia and those with idiopathic thrombopenic purpura developed remissions under treatment with ACTH or cortisone. The reports stressed the necessity of adequate dosage. Dameshek has indicated his belief that this method of treatment has definitely reduced the necessity for splenectomy in the vast majority of cases and he has indicated the desirability of careful and repeated trial of the hormones in such cases before splenectomy is recommended.

Antibiotics

All over the world the search continues for new antibiotics. A report from The Upjohn Company indicated that a new antibiotic, Albamycin, had been found in soil samples collected in Queens Village, New York. This substance is derived from *Streptomyces niveus* and the drug was given the name of Streptonivicin as a generic term. The special claims made for the product are that it may take over when other longer-used antibiotics have failed and that it may establish high blood levels.

Stylomycin is a new antibiotic developed by Lederle and apparently tried in 15 cases of trypanosomiasis with some success. This drug was formerly called puromycin. Bristol Laboratories has one called Amphomycin for the same purpose; Merck has one called Cathomycin and Squibb's is Thiostepton.

New in the use of antibiotics is employment of a combination of nystatin, a new antifungal antibiotic, with tetracycline in the treatment of a number of conditions. The advantage of such a mixture is said to be its ability to prevent the invasion of various fungi following elimination of bacteria by antibiotics. Investigators reported that a combination of oxytetracycline and neomycin antibiotics did not prevent fungal overgrowth but that the combination was effective in eradicating *Proteus* organisms as an invader. Studies were made on the combination of nystatin and tetracycline under the name of Mysteclin and it was found effective in a variety of bacterial infections.

APC Infection

An outbreak occurred in many portions of the United States, and also in other countries, of a condition involving inflammation of the adenoids, the pharynx and the conjunctiva. In a study of this condition, nine different viruses were found, all of them respiratory viruses. Type 3 APC virus causes a five day illness with fever, sore throat and conjunctivitis. This was the form most prevalent in children's summer camps. Investigators of the United States Public Health Service, National Institutes of Health, prepared a vaccine which was used in 45 persons who were shown by tests to have little or no antibodies in their blood against type 3 APC virus. Further epidemiologic studies are necessary to determine the effectiveness of a multistrain vaccine and this work is considered to be still in an experimental stage.

MORRIS FISHBEIN

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